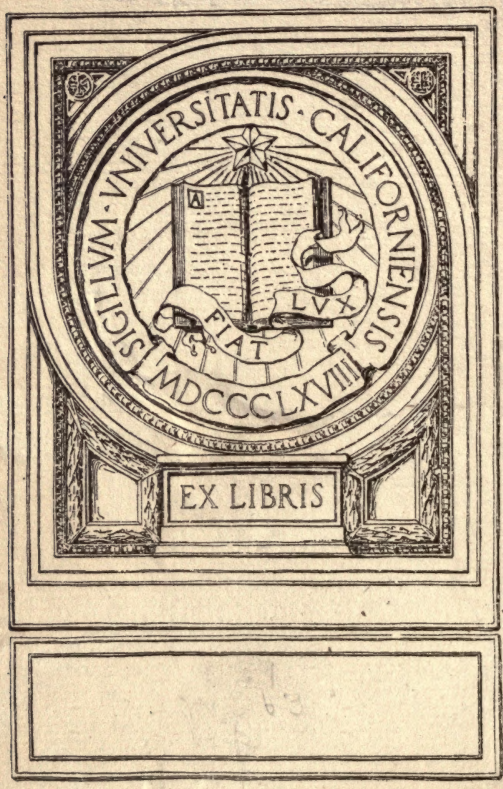








Sheffield Laboratory of Yale University

PAPERS ON PYRIMIDINES

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TO VINT
ADDRESS

PREFACE

In the present volume the Authors have incorporated all the Papers on Pyrimidines, which have appeared from the Sheffield Laboratory prior to the year 1910.

A bibliography of publications on pyrimidines, arranged chronologically, has also been appended to this book, but it must be understood that it is not intended to be complete. The aim of the authors has been to furnish a guide to readers, who are unacquainted with pyrimidine literature, rather than to give a complete list of publications in this field.

H. L. W. and T. B. J.

Sheffield Laboratory, New Haven.
January, 1910.

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- SYNTHESES OF AMINOXYPRIMIDINES HAVING THE COMPOSITION OF CYTOSINE: 2-AMINO-6-OXYPYRIMIDINE AND 2-OXY-6-AMINOPYRIMIDINE. By Henry L. Wheeler and Treat B. Johnson. (*American Chemical Journal*, 1903, XXIX, 492).
- ON CYTOSINE OR 2-OXY-6-AMINOPYRIMIDINE FROM TRITICNUCLEIC ACID. By Henry L. Wheeler and Treat B. Johnson. (*American Chemical Journal*, 1903, XXIX, 505).
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- THE ACTION OF POTASSIUM THIOCYANATE UPON SOME IMIDE-CHLORIDES. By Henry L. Wheeler and H. Stanley Bristol. (*American Chemical Journal*, 1905, XXXIII, 448).
- THE ACTION OF AQUEOUS AND ALCOHOLIC AMMONIA AND ANILINE ON SOME HALOGEN AND MERCAPTO PYRIMIDINES. By Treat B. Johnson and Carl O. Johns. (*American Chemical Journal*, 1905, XXXIV, 175).

- 2-ETHYLMERCAPTO-5-AMINO-6-OXYPYRIMIDINE. By Treat B. Johnson. (*American Chemical Journal*, 1905 XXXIV, 191).
- ON 2, 5-DIAMINO-6-OXYPYRIMIDINE. By Treat B. Johnson and Carl O. Johns. (*American Chemical Journal*, 1905, XXXIV, 554).
- SOME 5-IODOPYRIMIDIN DERIVATIVES: 5-IODOCYTOSINE. By Treat B. Johnson and Carl O. Johns. (*Journal of Biological Chemistry*, 1906, I, 305).
- ON METHODS OF SYNTHESIZING ISOBARBITURIC ACID AND 5-OXYCYTOSIN. By Treat B. Johnson and Elmer V. McCollum. (*Journal of Biological Chemistry*, 1906, I, 437).
- THE ACTION OF POTASSIUM THIOCYANATE UPON IMIDE CHLORIDES. By Treat B. Johnson and Elmer V. McCollum. (*American Chemical Journal*, 1906, XXXVI, 136).
- ON THE FORMATION OF PURINES FROM UREAPYRIMIDINES. By Treat B. Johnson and Elmer V. McCollum. (*American Chemical Journal*, 1906, XXXVI, 149).
- ON 5-NITROCYTOSINE AND ITS REDUCTION TO 2-OXY-5, 6-DIAMINOPYRIMIDINE. By Treat B. Johnson, Carl O. Johns and Frederick W. Heyl. (*American Chemical Journal*, 1906, XXXVI, 160).
- 5-ETHYLCYTOSIN. By Treat B. Johnson and George A. Menge. (*Journal of Biological Chemistry*, 1906, II, 105).
- SYNTHESIS OF URACIL-5-CARBOXYLIC ACID. By Henry L. Wheeler, Treat B. Johnson and Carl O. Johns. (*American Chemical Journal*, 1907, XXXVII, 392).
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- URACIL-4-CARBOXYLIC ACID. By Henry L. Wheeler. (*American Chemical Journal*, 1907, XXXVIII, 358).
- THE ACTION OF METHYL IODIDE ON 2-ANILINO-6-OXYPRIMIDINE, AND THE SYNTHESIS OF 2-ANILINOPYRIMIDINE. By Treat B. Johnson and Frederick W. Heyl. (*American Chemical Journal*, 1907, XXXVIII, 237).

- SYNTHESIS OF THYMIN-4-CARBOXYLIC ACID By Treat B. Johnson. (*Journal of Biological Chemistry*, 1907, III, 299).
- SYNTHESIS OF CYTOSINE-5-CARBOXYLIC ACID. By Henry L. Wheeler and Carl O. Johns. (*American Chemical Journal*, 1907, XXXVIII, 594).
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- SYNTHESIS OF 4-METHYLURACIL-5-ACETIC ACID. By Treat B. Johnson and Frederick W. Heyl. (*American Chemical Journal*, 1907, XXXVIII, 659).
- A METHOD OF SEPARATING THYMIN FROM URACIL. By Treat B. Johnson. (*Journal of Biological Chemistry*, 1908, IV, 407).
- THE ACTION OF NITRIC ACID ON 2, 6-DIOXYPYRIMIDINES. OXY-NITROHYDROTHYMIN. By Treat B. Johnson. (*American Chemical Journal*, 1908, XL, 19).
- SYNTHESIS OF URACIL-3-ACETIC ACID. By Henry L. Wheeler and Leonard M. Liddle. (*Journal American Chemical Society*, 1908, XXX, 1152).
- SYNTHESIS OF URACIL-4-ACETIC ACID. By Henry L. Wheeler and Leonard M. Liddle. (*Journal American Chemical Society*, 1908, XXX, 1156).
- SYNTHESIS OF SOME NITROGEN-ALKYL DERIVATIVES OF CYTOSIN, THYMIN AND URACIL. By Treat B. Johnson and Samuel H. Clapp. (*Journal of Biological Chemistry*, 1908, V, 49).
- THE ACTION OF DIAZO-BENZENE SULFONIC ACID ON THYMIN, URACIL AND CYTOSIN. By Treat B. Johnson and Samuel H. Clapp. (*Journal of Biological Chemistry*, 1908, V, 163).
- THE ACTION OF POTASSIUM THIOCYANATE UPON SOME IMIDE CHLORIDES. By Treat B. Johnson and Walter F. Storey. (*American Chemical Journal*, 1908, XL, 131).
- SYNTHESIS OF CYTOSINE-5-CARBOXAMIDE. By Henry L. Wheeler and Carl O. Johns. (*American Chemical Journal*, 1908, XL, 233).
- SYNTHESIS OF SOME BENZYL DERIVATIVES OF URACIL AND THYMINE. By Treat B. Johnson and John H. Derby, Jr. (*American Chemical Journal*, 1908, XL, 444).
- SYNTHESIS OF NEW DERIVATIVES OF 5-HYDROXYURACIL (ISOBARBITURIC ACID. By Treat B. Johnson and D. Breese Jones. (*American Chemical Journal*, 1908, XL, 538).

- THE THIO DERIVATIVES OF URACIL AND THE PREPARATION OF URACIL IN QUANTITY. By Henry L. Wheeler and Leonard M. Liddle. (*American Chemical Journal*, 1908, XL, 548).
- ON THE FORMATION OF PURINE DERIVATIVES FROM 4-METHYL-CYTOSINE. By Carl O. Johns. (*American Chemical Journal*, 1909, XLI, 58).
- SYNTHESIS OF 1-METHYL-5-HYDROXYURACIL. By Treat B. Johnson and D. Bresse Jones. (*Journal American Chemical Society*, 1909, XXXI, 591).
- THE PREPARATION OF 3-METHYL- AND 3-BENZYLURACIL. By Henry L. Wheeler and Treat B. Johnson. (*American Chemical Journal*, 1909, XLII, 30).
- THE PREPARATION OF 1, 4-DIMETHYLURACIL AND OF THE MONOBENZYL DERIVATIVES OF 4-METHYLURACIL. By Henry L. Wheeler and David F. McFarland. (*American Chemical Journal*, 1909, XLII, 101).
- SULPHUR DERIVATIVES OF 5-HYDROXYURACIL: PREPARATION OF 5-BENZYL MERCAPTOURACIL AND 5-BENZYL MERCAPTOCYTOSINE. By Treat B. Johnson and Herbert H. Guest. (*American Chemical Journal*, 1909, XLII, 271).
- DIMETHYL DERIVATIVES OF 2-AMINOPYRIMIDINE. PREPARATION OF 2-METHYLAMINO-5-METHYLPYRIMIDINE. By Treat B. Johnson and Kenneth G. Mackenzie. (*American Chemical Journal*, 1909, XLII, 353).
- THE ACTION OF METHYL IODIDE AND OF BENZYL CHLORIDE UPON 2-OXY-4-METHYL-6-METHYLMERCAPTOPYRIMIDINE. By Henry L. Wheeler and David F. McFarland. (*American Chemical Journal*, 1909, XLII, 431).
- SYNTHESIS OF 5-CYANURACIL. By Treat B. Johnson. (*American Chemical Journal*, 1909, XLII, 505).
- THE THIO DERIVATIVES OF THYMINE AND THE PREPARATION OF THYMINE. By Henry L. Wheeler and David F. McFarland. (*American Chemical Journal*, 1910, XLIII, 19).
- ON SOME PICROLONATES. By Henry L. Wheeler and George S. Jamieson. (*Journal of Biological Chemistry*, 1908, IV, 111).

APPENDIX

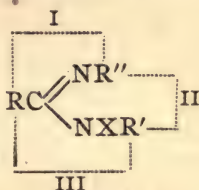
Bibliography of Pyrimidine Literature.

Contributions from the Sheffield Laboratory of Yale University.

LX.—RESEARCHES ON THE CYCLOAMIDINES : PYRIMIDINE DERIVATIVES.

BY H. L. WHEELER.

For convenience of reference, in this work, those compounds which have the amidine formation



in which two of the radicals R, R', and R'' are replaced by a ring structure or a bivalent grouping, are referred to as cycloamidines. The dotted lines in the above formula show the three possible ways of replacing the radicals, and they indicate three forms of cycloamidines. It will be noticed, however, that III is the tautomeric form of I. The tautomeric form of II being obtained when the position of the hydrogen X is changed to the opposite nitrogen atom. There are therefore only two types of cycloamidines, each type having a pseudomeric or tautomeric form as in the case of the simple amidines.

The *first type*, which contains only one of the nitrogen atoms in the ring is represented by such compounds as α -aminoquinoline, the α -aminobenzoxazines, etc.

The *second type*, with both nitrogen atoms in the ring structure, is found in the anhydro bases, glyoxalines, lophin, etc.

Then, further, combinations of these types and their tautomeric forms occur : The cyanalkines, α -amino- and anilidopyrimidines, aminoquinoxalines, cyanuramide, dicyanorthophenylenediamines, and the like, are examples of the combination types.

The object of the work, of which this paper gives a preliminary account, is primarily to investigate the action of alkyl halides on some of these cycloamidines which have not yet been examined in this respect, and also to compare this action in general with that of the simple amidines.

Pechmann¹ assumes that when a simple amidine, represented by the general formula above, is acted on with alkyl iodides, the hydrogen X is directly replaced, and hence this reaction serves to determine structure.

It seems to the writer that alkyl iodides may be added either to the amido group or to the imido group or, when the substituents are similar,² to both and perhaps to the atoms joined by double union. In two of the latter cases an amidine would result of a different structure from that obtained by direct substitution, so that this method of determining structure seems to be not without objection.

The cycloamidines, in general, unite with alkyl iodides and a number of cases have been described among those of the first type, where no direct substitution or replacement of hydrogen in the amino group takes place, at least not as the first step of the reaction. To illustrate this the following may be cited: Thiele and Ingle³ obtained dialkylaminotetrazols by the action of alkyl iodides on aminotetrazol. They believe that in these only one of the alkyl groups replaces hydrogen of the amino group. Claus⁴ shows that α -aminoquinoline takes up alkyl iodides in the same manner as the quinoline and pyridine bases in general, and that the amino-hydrogen is not substituted. Again, E. v. Meyer⁵ has shown in several cases that the cyanalkines form similar addition-products, the amino group not being substituted.

Even acyl chlorides add to the cyanalkines without substituting the amino group. Herfeldt⁶ found that cyanbenzylin or aminophenyldibenzylmiazin unites with acetyl and benzoyl

¹ Ber. d. chem. Ges., **28**, 2362 and 869.

² Pechmann (*loc. cit.*) found that when the substituents are similar radicals, the amidine gave two isomeric alkylated products. This is precisely what would be expected if the action is one of addition. There being in that case no decided tendency to addition entirely to either one of the nitrogen atoms.

³ Ann. Chem. (Liebig), **287**, 249.

⁴ J. prakt. Chem., **17**, 209.

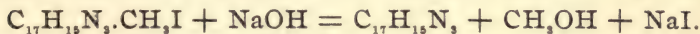
⁵ *Ibid.* **22**, 266, and **39**, 265.

⁶ *Ibid.* [2], **53**, 249.

chlorides to form well crystallized addition-products, and that an acetyl or benzoylcyanbenzylin was not obtained. In these cases it is a tertiary nitrogen which is the point of attack or addition.

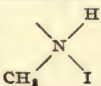
The action of alkyl iodides on the cycloamides of the second type is that of addition also, and, as in the case of the simple amidines, this action has generally been considered to be a direct replacement of hydrogen, since by treating the addition-product with alkali alkyl compounds result. The same question arises here as in the case of the simple amidines. That the alkyl group invariably replaces the hydrogen, however, has not been proved. It is not improbable that, like the cycloamidines of the first class, it is the tertiary nitrogen that unites with the alkyl halide.

The writer has found that phenylmethylanilidopyrimidine acts with methyl and ethyl iodides forming stable addition-products, and that no substitution takes place, that the alkyl iodide unites with one of the tertiary nitrogen atoms of the ring and not with the anilido group follows in all probability from the behavior of these products with alkali :

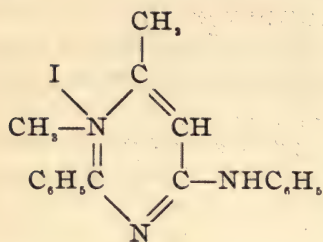


That is, methyl alcohol and sodium iodide are quantitatively formed, and unaltered anilidopyrimidine is regenerated. The formula that appears most probable for these addition-products is therefore either I or II, and from analogy a similar structure might be expected in the case of the alkyl halogen addition-products of the simple amidines.¹

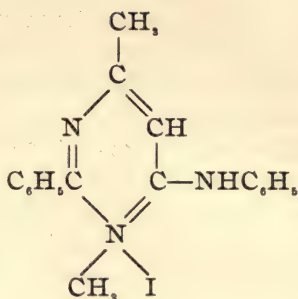
¹ The fact that the alkyl iodide addition-products of the simple amidines give up hydrogen iodide and not the alkyl group as above cannot be considered as showing that the addition takes place to the $-NH-$ group of the amidine. To be sure, the

grouping  would be expected to give up hydrogen iodide, and those

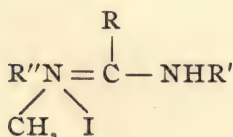
alkyl iodide addition-products of the cycloamidines which do not separate hydrogen iodide most probably do not have this grouping. But it cannot be maintained that because an addition-product gives up hydrogen iodide, it has this grouping.



I



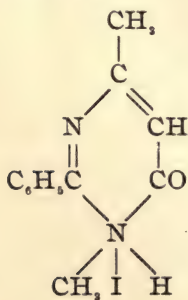
II



III

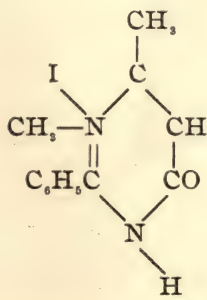
This being the case, the structure of the simple amidines must be completely revised, and the opposite or so-called tautomeric structure must be assigned to them. At any rate, no method has yet been devised for determining the structure of the amidines in question that is without objection.

It will be shown below that phenylmethylpyrimidon, a cycloamidine of the second type, unites with one molecule of methyl iodide to form a beautiful crystalline addition-product of formula IV or V.



IV

or



V

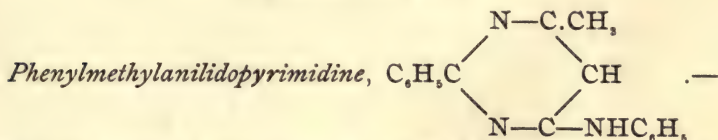
This compound, on treatment with alkali, gives up hydrogen iodide and not the alkyl group, and an alkylated pyrimi-

don results. This alkyl derivative differs decidedly from the product obtained by heating phenylmethylchlorpyrimidine with sodium methylate. The alkyl iodide therefore is added to one of the nitrogen atoms of the pyrimidon ring, while Pinner¹ found that, if the oxypyrimidine is heated with ethyl iodide in the presence of alkali, the ethyl group attaches itself to oxygen.

In order to determine to which nitrogen the alkyl halide is added, a synthesis of the methylpyrimidon was attempted as follows: Methylbenzamidine hydrochloride was prepared. This, with acetoacetic ester, according to Pinner's explanation of the formation of the pyrimidines, might be expected to give the base corresponding to formula IV. It was found, however, that methylbenzamidine does not give a pyrimidine derivative with acetoacetic ester, at least not under the same conditions that benzamidine does, so that for the present the question of the position of the alkyl group must be left undecided.

Nef² has shown that carbostyryl is not acted on by ethyl iodide. The above pyrimidon differs from carbostyryl, in its ring structure, in having a tertiary nitrogen. It would seem most probable therefore that it is due to this that the substance takes up methyl iodide and that the addition-product is perhaps best represented by formula V.

Experimental Part.



This was prepared according to Pinner's³ directions by warming phenylmethylchlorpyrimidine with aniline. Instead of purifying the material by dissolving the reaction-product in alcohol and precipitating it with ether, it was found best to crystallize it directly from water, precipitate the base from the hot aqueous solution and then crystallize this from benzene and alcohol. The material thus obtained crystallizes in

¹ Die Imidoäther und ihre Derivate, p. 343. ² Ann. Chem. (Liebig), 276, 242.

³ Die Imidoäther und ihre Derivate, p. 248.

clusters of small prisms and melts at 160° – 161° . Pinner gives its melting-point as 150° – 153° .

The *hydrochloride* was obtained in colorless needles melting at 240° as described by Pinner.

The *hydrobromide* was obtained by precipitating the base from a benzene solution with hydrobromic acid gas. It forms minute needles when crystallized from alcohol and it melts at 250° .

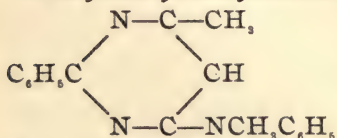
The *hydroiodide* forms colorless needles melting at 231° .

Phenylmethylanilidopyrimidine methyl iodide.—Six grams of the above cycloamidine were heated with an excess of methyl iodide in methyl alcohol solution for seven hours from 100° – 105° . The material was then washed with alcohol and crystallized from water and alcohol. Thus obtained, the substance melts at about 210° – 213° with strong effervescence. If suddenly heated it melts much lower. The material dried in the air contains 2 molecules of water of crystallization. [Analysis I. and II.] When dried at a temperature of 130° it was obtained anhydrous [Analysis III.]. Determinations I. and III. were made by dissolving the substance in water and precipitating with silver nitrate. Determination II. was made by the method of Carius.

	Calculated for			Found.		
	$C_{18}H_{18}N_2I_{1.2}H_2O$.	$C_{18}H_{18}N_2I$.		I.	II.	III.
I	28.9	31.5		28.8	28.7	31.5

This addition-product is readily soluble in warm water and in alcohol, from which it crystallizes in fine, colorless needles. Ammonia or alkali immediately precipitates a substance melting at 160° – 161° , which has all the properties of phenylmethylanilidopyrimidine.

Phenylmethylethylanilidopyrimidine,



—This was prepared by warming

phenylmethylchlorpyrimidine with methyl aniline. It is the compound that should result by treating the above addition-product with alkali, if the action of methyl iodide on the

cycloamidine takes place by substitution. A comparison of the above with the following properties show that these compounds are different. This compound crystallizes from alcohol in colorless prisms which melt at 113° . It dissolves readily in ether, alcohol, and benzene, but is insoluble in water. A nitrogen determination gave :

	Calculated for $C_{18}H_{17}N_3$.	Found.
N	15.2	15.0

This compound dissolves readily in dilute hydrochloric acid, and platinum chloride gives a bright yellow, granular precipitate, which melts at about 228° , with effervescence.

The *hydroiodide* is readily soluble in warm alcohol, less readily in water. It melts when slowly heated at about 198° . An iodine determination gave :

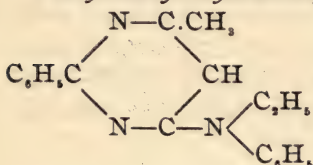
	Calculated for $C_{18}H_{18}N_3I \cdot 2H_2O$.	Found.
I	28.9	28.9

The *nitrate* separates from dilute nitric acid in long, colorless needles or prisms, which melt with violent effervescence at about 170° .

Phenylmethylanilidopyrimidine ethyl iodide.—This was obtained when 5 grams of phenylmethylanilidopyrimidine were heated with 10 grams of ethyl iodide for twelve hours at 120° – 130° . The reaction-product was extracted with hot water and then crystallized from alcohol, when it separated in colorless needles melting at about 215° . When crystallized from water the material shrivels at about 115° , then melts with effervescence at or near 215° . An iodine determination of air-dried material indicates that the substance separates with 1 molecule of water of crystallization. [Analysis I.] The material dried at 120° – 130° becomes anhydrous. [Analysis II.]

	Calculated for $C_{19}H_{20}N_3I \cdot H_2O$.	Calculated for $C_{19}H_{20}N_3I$.	Found. I.	Found. II.
I	29.19	30.4	29.24	30.3

This addition-product and the analogous methyl compound give off the methyl iodides when heated to their melting-points. Ammonia or alkali precipitate phenylmethylanilidopyrimidine from aqueous or alcoholic solutions.

Phenylmethylethylanilidopyrimidine,

.—This was prepared like the cor-

responding methylanilidopyrimidine for the sake of comparison with the base obtained from the above addition-product. It is an entirely different base. This melts at 87° when crystallized from alcohol. It is readily soluble in hot alcohol, difficultly in cold, and insoluble in water. It separates in beautiful, long, colorless prisms. A nitrogen determination gave :

	Calculated for $\text{C}_{19}\text{H}_{19}\text{N}_3$.	Found.
N	14.53	14.56

The *hydrochloride* is difficultly soluble in cold water, readily in hot, and crystallizes in colorless needles which appear to be hydrous. On heating the material shrivels at about 100° , then melts at about 210° .

The *platinum chloride salt* separates as a bulky, light-yellow precipitate. It is insoluble in hot water, and melts at about 218° .

The *hydroiodide* crystallizes in prisms.

An attempt to prepare an ethyl bromide addition-product of phenylmethylanilidopyrimidine was unsuccessful. 3.8 grams of anilidopyrimidine were heated with an excess of ethyl bromide from 102° – 104° for five hours, when the material was found to be unaltered. It was heated again, this time with the addition of some alcohol, the temperature being kept between 120° – 130° for seventeen hours. On opening the tube then, the products were found to be the hydrobromide of phenylmethylanilidopyrimidine described above, and ether. Ethyl bromide, therefore, neither effects substitution nor addition.

Phenylmethylpyrimidon methyl iodide.—Phenylmethoxy-pyrimidine and methyl iodide, 4 grams of the former and 10 of the latter, were heated for six hours at 100° . No reaction was evident. The material was then heated for nine hours at

170°, when addition took place. The material dissolved almost entirely in water and, on concentrating the aqueous solution to a syrup, a mass of needles was obtained. This was crystallized from alcohol when beautiful, large, colorless prisms separated. These did not melt sharply, but decomposed with effervescence at 230°. An iodine determination gave :

	Calculated for $C_{11}H_{10}N_2O.CH_3I.$	Found.
I	38.7	38.6

n-Methylphenylmethylpyrimidon.—When the above compound with methyl iodide was dissolved in a little water and dilute alkali was added, this compound separated as a mass of colorless needles. It was purified by crystallizing from water, when it separated in the form of beautiful, large prisms, which melt at about 91°–92°. A nitrogen determination gave :

	Calculated for $C_{12}H_{12}N_2O.$	Found.
N	14.0	13.6

This compound has basic properties ; it dissolves readily in dilute acids, the ordinary salts being all quite soluble. It is readily soluble in alcohol and ether, less readily in water, and is not dissolved by a small amount of alkali. The nitrate and platinum chloride double salt are the least soluble of the ordinary salts. These were obtained by spontaneous evaporation of the solutions.

The *nitrate* crystallizes in colorless, flattened prisms which melt with effervescence at about 195°.

The *platinum chloride* double salt separates in form of very large prisms with the color of azobenzene. It gave no definite melting-point below 275°, but turned dark at about 235°.

Methylbenzamidine hydrochloride, $C_6H_5C(NH)NHCH_3.HCl$.—This was prepared by dissolving benzimidoethylester hydrochloride in a 33 per cent. solution of methylamine. On adding the hydrochloride to the solution of the amine the free ester separates ; on shaking this dissolves, and in a short time a mass of colorless needles separates. This material was crystallized from water in which it is not extremely soluble. A chlorine determination gave :

	Calculated for $C_8H_{10}N_2.HCl.$	Found.
Cl	20.82	20.75

The properties of this amidine hydrochloride apparently differ decidedly from those of the corresponding ethylamidine. Lossen¹ prepared ethylamidine hydrochloride in a state of purity only with some difficulty, while Pinner² obtained the hydroiodide as an oil which would not crystallize.

NEW HAVEN, March, 1898.

¹ Ann. Chem. (Liebig) **265**, 159.

² Ber. d. chem. Ges., **11**, 7.

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MAY, 1903.]

Contributions from the Sheffield Laboratory of Yale University.

CII.—ON SOME CONDENSATION-PRODUCTS OF THE PSEUDOTHIUREAS: SYNTHESIS OF URA- CIL, THYMINE, AND SIMILAR COM- POUNDS.

BY HENRY L. WHEELER AND HENRY F. MERRIAM.

Urea and thiourea have been shown to undergo condensation with a variety of substances, but apparently no one has attempted to use the simple pseudothiureas in any synthetic process whatever.¹

The pseudothiureas in question, $\text{HN}=\text{C}(\text{SR})-\text{NH}_2$, ($\text{R}=\text{CH}_3-$ or C_2H_5-), have not been isolated. Their halogen hydride salts result from the addition of alkyl halides to thiourea. These are described as extremely unstable compounds, and Claus² states that when the ethyl bromide addition-prod-

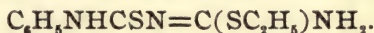
¹ Rathke has shown that their salts give guanidine when boiled with ammonia. *Ber. d. chem. Ges.*, **17**, 309 (1884).

² *Ann. Chem. (Liebig)*, **179**, 146 (1875).

uct is treated with alkali it decomposes into ethyl rhodanide, ammonia, and hydrogen bromide.

In the case of the methyl iodide addition-product, Bernthsen and Klinger¹ found that, with silver oxide, a solution containing a strong base resulted, which gave a blue color to red litmus. This base was supposed to be a hydroxyl compound, $\text{H}_2\text{NCSNH}_2\cdot\text{CH}_3\text{OH}$, which, on evaporating in a desiccator, decomposed. The ethyl iodide addition-product, which Claus describes as an exceptionally unstable compound,² under similar treatment with silver oxide gave a strong alkaline solution which, on evaporation, contained cyanamide (dicyandiamide). A similar decomposition was observed when the compounds were treated with mercuric oxide.

We have made no attempts to isolate these free pseudothioureas, but, at first, in order to obtain an idea of their stability, we treated the methyl iodide addition-product in aqueous solution with an excess of alkali and benzoyl chloride, and obtained an excellent yield of the corresponding benzoylpseudothiourea,³ $\text{C}_6\text{H}_5\text{CON}=\text{C}(\text{SCH}_3)-\text{NH}_2$. The ethyl bromide addition-product, on shaking with alkali and phenyl mustard oil, gave a good yield of the phenylpseudodithiobiuret,



The free pseudothioureas are, therefore, not so unstable as one might be led to believe from previous work, and, owing to their strong basic nature, it seemed probable that they would undergo condensation with aldehyde and ketone esters more readily, and prove more reactive in general, than the normal ureas. This we have found to be the case.

Ernert⁴ states that urea does not condense with the substituted acetoacetic esters or with benzoylacetic ester. Warmington,⁵ also, was unable to obtain a condensation of urea and the latter ester, in aqueous solution, but found that they could be condensed in the dry state at a high temperature.

We have readily obtained such condensations with the

¹ Ber. d. chem. Ges., **11**, 493 (1878).

² *Ibid.*, **8**, 41 (1875).

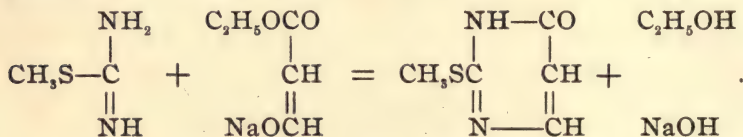
³ J. Am. Chem. Soc., **23**, 293 (1901).

⁴ Ann. Chem. (Liebig), **258**, 362 (1890).

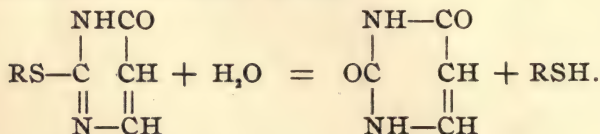
⁵ J. prakt. Chem., [2], **47**, 202 (1893).

pseudothiureas at ordinary temperatures. These pyrimidine condensations, which are analogous to Pinner's,¹ take place in alkaline solution in a similar manner to that observed by Michael in the case of urea with acetoacetic and malonic esters.² They are also similar to Traube's synthesis of pyrimidine derivatives in which guanidine and ethyl cyanacetate are employed.³

A method similar to that of preparing methyluracil by condensing urea with acetoacetic ester, by means of hydrochloric acid,⁴ has not been applied to the preparation of uracil, probably on account of the ease with which free formylacetic ester passes into trimesic ester. On the other hand, the sodium salt of formylacetic ester is not only easily prepared,⁵ but is also quite stable, and we have found that it readily condenses, in aqueous solution, with both methyl- and ethyl-pseudothiureas, giving a good yield of the corresponding methyl- and ethyl-mercaptopuracils. For example, with methyl-pseudothiurea, as follows:⁶



In order to obtain a practically quantitative yield of uracil from these compounds, heating with acids in a sealed tube is not necessary.⁷ When they are boiled with concentrated hydrochloric acid, or better with hydrobromic acid, they evolve mercaptan and yield uracil as follows:



¹ "Die Imidoäther u. ihre Derivate," p. 209.

² J. prakt. Chem., **35**, 456 (1887).

³ Ber. d. chem. Ges., **33**, 1371 (1900).

⁴ Behrend: Ann. Chem. (Liebig), **229**, 9; **251**, 238.

⁵ Wislicenus: Ber. d. chem. Ges., **20**, 2933 (1887).

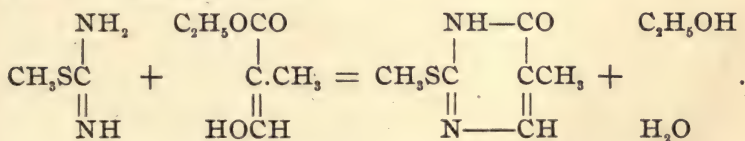
⁶ An attempt to condense urea with this salt gave a negative result.

⁷ List has shown that 2-methylmercapto-4-methyluracil gives 4-methyluracil when heated with concentrated hydrochloric acid at 180°. Ann. Chem. (Liebig), **236**, 12 (1886).

Emil Fischer and Georg Roeder¹ have recently prepared uracil, thymine, and other pyrimidine derivatives by means of an interesting synthesis. Their method consists in heating urea with unsaturated acids and brominating the hydrouracils thus formed. The bromine derivatives are then converted into uracils by treatment with alkali or pyridine. This synthesis has the disadvantage that the unsaturated acids are not in all cases easily accessible compounds, and the yields, especially in the case of uracil, are below those obtained by our method.

Uracil prepared by our method agreed in all respects with the description given by Fischer and Roeder. We have found that sodium acetoacetic ester and pseudomethylthiourea give 2-methylmercapto-4-methyluracil, which List² has prepared by a different method. This, on boiling with hydrobromic acid, gave Behrend's³ 4-methyluracil.

The isomeric 2-methylmercapto-5-methyluracil and 5-methyluracil, or thymine, were obtained in a similar manner. Free ethyl formylpropionate directly condensed with pseudomethylthiourea, and the sodium salt was also caused to react with the pseudothiourea :



On boiling this mercapto derivative with hydrochloric acid we obtained thymine, which was identical in all respects with the natural product obtained from the nucleic acid of the spleen, a sample of which, through the kindness of Dr. P. A. Levene, was sent to us for comparison. When the samples were mixed the melting-point was not altered.

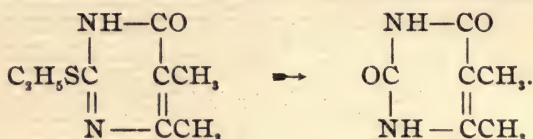
With the sodium salt of ethyl benzoylacetate and pseudomethylthiourea we obtained 2-methylmercapto-4-phenyluracil, which was converted by acids into 4-phenyluracil, identical with the phenyluracil described by Fischer and Roeder.

¹ Ber. d. chem. Ges., **34**, 3751 (1901).

² Ann. Chem. (Liebig), **236**, 12 (1886).

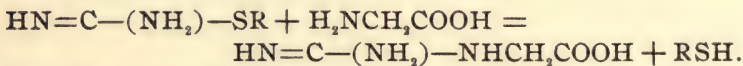
³ Ibid., **229**, 8.

With ethyl methylacetoacetate and pseudoethylthiourea we prepared 2-ethylmercapto-4,5-dimethyl-6-oxypyrimidine, which gave a new dimethyluracil (4,5-dimethyluracil) :



With ethyl ethyl-acetoacetate we prepared 2-methylmercapto-4-methyl-5-ethyl-6-oxypyrimidine and 4-methyl-5-ethyluracil. Like urea,¹ pseudomethylthiourea readily condenses with acetylacetone and two products are formed. It condenses also with ethyl cyanacetate.

Beside the above condensations, which involve an attachment to the two nitrogen atoms of the pseudothiourea, another type occurs in which only one nitrogen and the mercapto group take part. For example, amino acids react with the pseudothioureas in aqueous solution to form guanidine acids :



Since by appropriate treatment these compounds can be converted by loss of water into the corresponding rings, it seems probable that the isocreatinine obtained by Thesen² from fish flesh (haddock) may be prepared by this method, using N-methylpseudomethylthiourea and aminoacetic acid.

We wish to reserve the study of the condensation-products of the pseudothioureas for this laboratory.

EXPERIMENTAL PART.

Our experiments with the pseudothioureas have been confined to pseudomethyl- and pseudoethylthiourea.

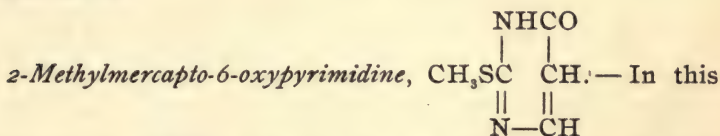
Pseudomethylthiourea hydriodide was prepared by moistening finely powdered thiourea with alcohol and then adding an excess of methyl iodide. Heat was evolved so that a condenser was necessary. After standing twelve hours, ether

¹ Evans : J. prakt. Chem., 48, 489 (1893).

² Hoppe-Seyler : Ztschr. physiol. Chem., 24, 4 (1898).

was added and the residue filtered, washed with ether, and dried. The crude addition-product thus prepared was used in the following experiments.

Pseudoethylthiourea hydrobromide, for use in these condensations, can be conveniently prepared from thiourea containing considerable ammonium thiocyanate; that is to say, from the product obtained by heating ammonium thiocyanate at 170° for forty-five minutes¹ and then crystallizing once or twice from water. The thiourea is powdered, moistened with alcohol, and an excess of ethyl bromide added. On boiling this mixture for four or five hours the greater part of the mass dissolves, leaving ammonium bromide as an insoluble residue. The solution is then filtered and most of the alcohol evaporated. The oil thus obtained is transferred to a distilling-bulb and the ethyl rhodanide distilled off under diminished pressure on the water-bath. The residue, on cooling, solidifies to a crystalline mass, which, after drying on paper in the air, melts at about 88° and is pure enough for use in the following experiments:



preparation the crude sodium salt of formylacetic ester² was considered as 70 per cent pure.³

Seven grams of sodium hydrate were dissolved in 70 cc. of water and 38 grams of the methyl iodide addition-product of thiourea were added, and then 29 grams of sodium formylacetic ester. The mixture was allowed to stand for twelve hours at ordinary temperature, then warmed on the water-bath for a few minutes, cooled, and acidified with acetic acid. The crystalline precipitate thus produced was filtered, washed, and dried. It weighed 11.3 grams, a yield of 46 per cent, calculating from the methyl iodide addition-product. It crystallized from water in long prisms, or short, lozenge-shaped

¹ Reynolds and Werner: J. Chem. Soc. (London), 83, 1 (1903).

² Wislicenus: Ber. d. chem. Ges., 20, 2933.

³ Von Pechmann: *Ibid.*, 25, 1047.

tablets, and the surfaces of the crystals were generally etched. It is quite soluble in alcohol and acetone, and it melts at 198° to 199°. A nitrogen determination gave :

	Calculated for $C_5H_5ON_2S$.	Found.
N	19.72	19.86
$ \begin{array}{c} \text{NH}-\text{CO} \\ \qquad \\ \text{C}_2\text{H}_5\text{SC} \quad \text{CH.} \\ \qquad \\ \text{N} \quad \text{CH} \end{array} $		
<i>2-Ethylmercapto-6-oxypyrimidine</i> , — Fifty-		

nine grams of the ethyl bromide addition-product of thiourea were treated with one molecular proportion of sodium hydrate in 10 per cent aqueous solution, and then 40 grams of formylacetic ester were added. After standing for twenty-four hours the solution was divided into two equal portions. One, after warming on the water-bath until effervescence stopped, was cooled and immediately acidified with acetic acid. This gave 6.3 grams of the mercapto derivative. The other portion was allowed to stand for a week. On acidifying then, 6.1 grams of the mercapto compound were obtained, a yield of 32 per cent of the calculated. In another experiment 25 grams of the ethyl bromide addition-product were dissolved in more dilute alkali, namely, 5.5 grams of sodium hydrate in 95 cc. of water, and 27 grams of sodium formylacetic ester were added. After two hours' standing, one-half of the solution was warmed, cooled, and acidified with acetic acid, whereupon 5 grams of the mercapto compound separated. After standing two days the remaining portion gave 4.9 grams of the condensation-product, a yield of 47 per cent of the calculated.

It is evident from this that the materials react in a short time, and that long standing does not influence the yield. The reaction possibly involves an addition similar to that in the case of acetoacetic ester and urea¹, since it frequently happens that these mixtures can stand for several days, and then, if the solution is not warmed before acidifying, no precipitation whatever occurs. Moreover, the fact that usually a yield

¹ Behrend and Ernert: Ann. Chem. (Liebig), **258**, 360 (1890).

approximating only one-half the calculated is obtained may also possibly be accounted for by the assumption that, like urea and acetoacetic ester in alkaline solution, 2 molecules of the ester react with only one of the pseudothiourea.

In one experiment, however, 5 grams of the ethyl bromide addition-product, 1.1 grams of sodium hydrate, and 6 grams of the sodium salt in 10 cc. of water, on standing over night, gave 2.9 grams of the condensation-product, a yield of 68.8 per cent of the calculated. On crystallizing from 10 cc. of alcohol, 1.75 grams of pure ethylmercaptopyrimidine separated at once. This substance is easily soluble in warm alcohol and hot water, difficultly soluble in cold, and forms beautiful, colorless, small, stout prisms and pyramids melting at 152°. A nitrogen determination gave:

N	Calculated for $C_4H_8ON_2S$.	Found.
	17.94	17.93

Uracil,	$ \begin{array}{c} \text{NH}-\text{CO} \\ \quad \\ \text{OC} \quad \text{CH} \\ \quad \\ \text{NH}-\text{CH} \end{array} $	—Fifteen grams of the above methyl-	X
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mercaptouracil and 150 cc. of concentrated hydrochloric acid were boiled for four hours, when mercaptan had ceased being evolved. The solution was evaporated to dryness and the residue, after drying, weighed 11.9 grams (94.4 per cent yield). It melted with effervescence at 335° (on an Anschütz thermometer in a paraffin-bath), and, on crystallizing from water, it formed balls of minute, pure-white needles, which, on rapidly heating, melted at 338°. By holding the temperature a few degrees below this the material could be made to melt. It agreed in properties with Fischer and Roeder's¹ preparation. When the ethylmercapto derivative (1.5 grams) was heated in a closed tube with concentrated hydrochloric acid (5 cc.) for four and one-half hours, about 0.05 gram of an insoluble by-product was formed, and 0.9 gram of pure uracil was obtained. A nitrogen determination gave:

¹ *Loc. cit.*

	Calculated for $C_4H_4O_2N_2$.	Found.
N	25.00	25.24

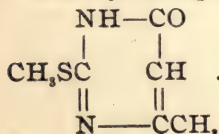
One hundred parts of water at 25° dissolve 0.358 part of uracil.

Uracil may be boiled with alkali and recovered unaltered by acidifying the solution. The alkaline solution probably contains the substance as a salt of β -uramidoacrylic acid, just as Behrend's methyluracil gives β -uramidocrotonic acid. When uracil is dissolved in ammonia and most of this removed by boiling, then silver nitrate is added and the solution is boiled, an amorphous silver salt is precipitated, which is soluble in an excess of ammonia and nitric acid. The composition of the salt prepared in this manner varied. One preparation gave 63.8 and 64 per cent silver, another 59.9 and 60.1 per cent silver, while the calculated for silver β -uramidoacrylate is 62.79 per cent. Uracil does not form a picrate.

5-Bromuracil.—Two and one-half grams of uracil were suspended in carbon disulphide and 3.8 grams of bromine were added. Hydrogen bromide was slowly evolved, and after two days, on evaporating to dryness, a red residue was obtained which, on warming on the water-bath, became colorless. When crystallized from water it formed small, stout, colorless prisms, and when heated turned dark above 200°, and melted with some effervescence at about 293°. A nitrogen determination gave :

	Calculated for $C_4H_3O_2N_2Br$.	Found.
N	14.66	14.60

2-Methylmercapto-4-methyl-6-oxypyrimidine,

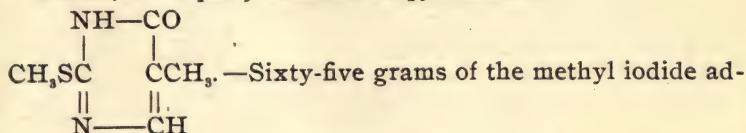


—Sixteen grams of the methyl iodide addi-

tion-product of thiourea were dissolved in 20 cc. of water and added to a cold 30 per cent solution of 4.5 grams of potassium hydrate. Nine and six-tenths grams of acetoacetic ester were then added and the mixture allowed to stand. The

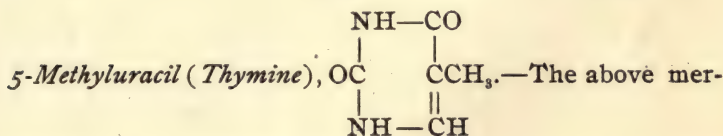
next day long prisms had formed. After two days these were filtered and found to weigh 5 grams. This material was soluble in acids and alkali, and it melted at 219° , the melting-point assigned to this compound by List. When 2 grams of this were boiled with 10 cc. of hydrobromic acid for one hour mercaptan was given off and 1.2 grams of Behrend's 4-methyluracil were obtained.

2-Methylmercapto-5-methyl-6-oxypyrimidine,



dition-product of thiourea were treated with 17 grams of potassium hydrate in 150 cc. of water, and 45 grams of sodium formylpropionic ester were then added. The mixture, on standing two and a half days, was filtered from some sediment and neutralized with acetic acid. A fine crystalline precipitate of methylmercaptothymine came down, which weighed 9.2 grams, or 20 per cent of the calculated. It crystallized in strings of small plates from water, in which it is difficultly soluble when hot and nearly insoluble when cold. On heating, it sintered at about 225° and melted at 233° . A nitrogen determination gave :

	Calculated for $\text{C}_6\text{H}_8\text{ON}_2\text{S}$.	Found.
N	17.94	17.95



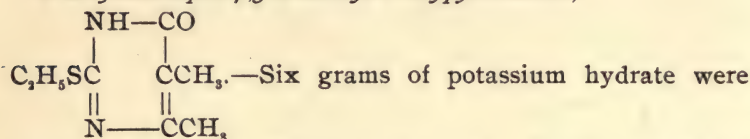
captothymine reacted less readily with hydrochloric acid than in the other cases. Nine and two-tenths grams were boiled with 100 cc. of concentrated hydrochloric acid for ten hours, whereupon no more mercaptan was given off. The solution, on evaporating, then gave 7.3 grams of crude thymine (melting at 319°), which is 99 per cent of the calculated. This crystallized from water in small, apparently rectangular, colorless

plates, and on rapidly heating melted at 326° (on an Anschütz thermometer). Fischer and Roeder state that their preparation sintered at 318° and melted at 321° . A sample of thymine which Dr. P. A. Levene, of the Pathological Institute at Ward's Island, N. Y., kindly gave us, proved to be identical with our compound. This sample was obtained from the nucleic acid of the spleen, and on mixing it with some of our substance the melting-point was unchanged. A nitrogen determination in the case of the synthetic product gave :

	Calculated for $C_8H_8O_2N_2$.	Found.
N	22.22	22.36

One hundred parts of water at 25° dissolve 0.404 part of thymine.

2-Ethylmercapto-4,5-dimethyl-6-oxypyrimidine,



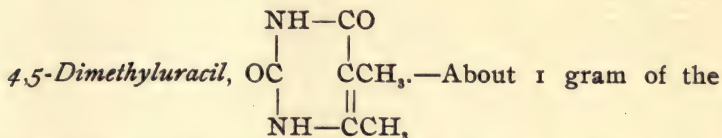
dissolved in 50 cc. of water and cooled. To this was added 13 grams of the ethyl bromide addition-product of thiourea and then 10 grams of methyl acetoacetic ester. The oil gradually disappeared and a white solid was formed. After standing for two days the solution was made slightly acid with hydrochloric acid and filtered. The precipitate in this case proved to be a mixture. On boiling with about 30 cc. of alcohol and filtering while hot, a separation was effected. The soluble portion was crystallized from a mixture of alcohol and ether. It formed stout prisms melting at about 156° , sintering at about 151° , and a nitrogen determination gave :

	Calculated for $C_8H_{12}ON_2S$.	Found.
N	15.2	15.6

The compound that was not readily dissolved by boiling alcohol was purified by crystallizing it from a large amount of alcohol. It was found to be free from sulphur, and on heating it began to decompose at about 260° , and effervesced at 269° to 270° , turning reddish-brown. It consisted of minute,

microscopic crystals that formed twins having the form of a cross. We did not stop to determine the structure of this compound, but we believe that possibly it is acetomethyl-acetylcyanamide, $\text{CH}_3\text{CO}(\text{CH}_3)\text{CHCONHCN}$. A nitrogen determination agreed with the calculated for this formula.

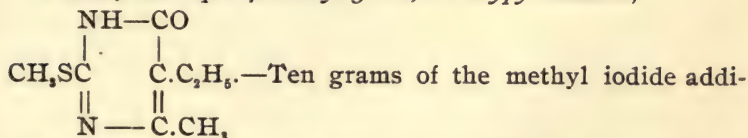
	Calculated for $\text{C}_6\text{H}_9\text{O}_2\text{N}_2$.	Found.
N	20.00	20.03



above ethylmercaptodimethyluracil was boiled for four hours with 10 cc. of concentrated hydrochloric acid. Mercaptan was given off and there was a smooth decomposition into the oxygen derivative. The solution was evaporated to dryness and the residue was crystallized twice from alcohol. It crystallized in microscopic needles which melted to a clear liquid, with partial decomposition, at 292° . A nitrogen determination gave :

	Calculated for $\text{C}_6\text{H}_9\text{O}_2\text{N}_2$.	Found.
N	20.00	20.34

2-Methylmercapto-4-methyl-5-ethyl-6-oxypyrimidine,



tion-product of thiourea were dissolved in a solution of 2.6 grams of potassium hydrate (1 molecule) in 20 cc. of water, and to this 7 grams of ethyl ethylacetoacetate were added. A little alcohol was also added, and finally some more alkali, and the mixture was allowed to stand for a week. Solid material gradually separated, which was filtered after neutralizing the solution. The yield of crude material was 3.2 grams. It was crystallized from alcohol, from which it separated in long, flat, colorless prisms with branching, brush-like

drate, and precipitated with carbon dioxide, it gave *o*-benz-glycocycamidine.¹

Pseudomethylthiourea Chloracetate,

$\text{H}_2\text{N}-\text{C}(\text{SCH}_3)=\text{NH}.\text{ClCH}_2\text{COOH}$.—Thirty-three grams of the methyl iodide addition-product of thiourea were dissolved in a small quantity of cool alcohol, and a concentrated alcoholic solution of 8.5 grams of potassium hydrate was added. The solution was filtered from potassium iodide and then 14.5 grams of chloracetic acid were slowly added. Crystalline material soon separated which, on drying, weighed 17 grams. When crystallized from alcohol it formed transparent, rectangular plates, melting at 162° . It was very soluble in water. A nitrogen determination gave:

	Calculated for $\text{C}_4\text{H}_9\text{O}_2\text{N}_2\text{SCl}$.	Found.
N	15.17	15.26

NEW HAVEN, CONN., Feb. 26, 1903.

¹ Griess: Ber. d. chem. Ges., 13, 977.

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MAY, 1903.]

Contributions from the Sheffield Laboratory of Yale University.

CIII.—SYNTHESES OF AMINOXYPYRIMIDINES
HAVING THE COMPOSITION OF CYTOSINE :
2-AMINO 6-OXYPYRIMIDINE AND 2-OXY-
6-AMINOPYRIMIDINE.

BY HENRY L. WHEELER AND TREAT B. JOHNSON.

The interest which in recent years has been attached to the study of pyrimidine derivatives has been increased by a new discovery of Kossel and Steudel. Working with a large quantity of sturgeons' testicles they obtained, in the histidine fraction, a basic substance agreeing in composition with the formula $C_4H_5ON_3$. Kossel and Steudel state their belief that this compound is an aminooxypyrimidine,² since hitherto all of the nitrogen compounds obtained from nucleic acid have been found to contain the pyrimidine ring. This new substance was found to closely resemble cytosine, which Kossel and Neumann³ obtained in the year 1894 as a cleavage-prod-

² Ztschr. physiol. Chem., **37**, 179 (1902).

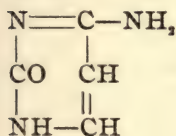
³ Ber. d. chem. Ges., **27**, 2215 (1894).

uct of thymus nucleic acid. Kossel and Steudel have recently undertaken the reinvestigation of thymus cytosine and they now¹ conclude that the product is identical with sturgeon cytosine. They state that it can also be prepared from herrings' testicles and call attention to the fact of its wide occurrence in animal organs.

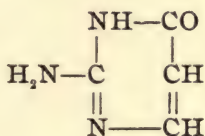
Dr. P. A. Levene has kindly sent us the proof of his article on "Darstellung und Analyse einiger Nucleinsäuren," in which he describes the preparation of this base from the nucleic acid of the spleen and pancreas.²

Kossel and Steudel³ conclude that material yielding uracil is widely disseminated in animal organs, and it seemed probable that perhaps uracil results from the cleavage of cytosine by treatment with sulphuric acid at high temperatures. Moreover, they state in their last paper⁴ that cytosine, by the action of nitrous acid, gives a substance having the properties of uracil.

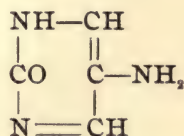
From this it appears that of the seven theoretically possible⁵ aminoxyypyrimidines, the first to be considered are those that would be expected to yield uracil by the above treatment. An examination of the following formulas will show that formulas I. and II. are the only ones that agree with this behavior :



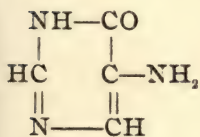
I.



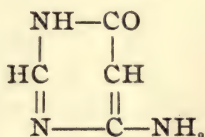
II.



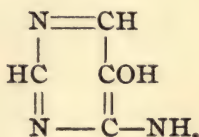
III.



IV.



V.



VI.

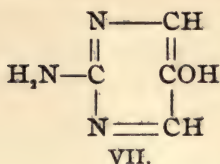
¹ Ztschr. physiol. Chem., **37**, 379 (1903).

² To appear in Ztschr. physiol. chem., **38**, (1903). See also Am. J. Physiol., **8**, XII (1903); J. Am. Chem. Soc., **25**, R. 188 (1903).

³ *Ibid.*, **37**, 247 (1903).

⁴ *Ibid.*, **37**, 380 (1903).

⁵ Tautomeric forms are not considered.



We have now prepared the two aminooxypyrimidines represented by formulas I. and II. and we find that both products agree closely in properties with the descriptions of cytosine. Of the two compounds, 2-oxy-6-amino-pyrimidine, formula I., agrees better than the isomer, 2-amino-6-oxypyrimidine. Formula II., in fact, seems to be excluded as representing cytosine chiefly because this compound crystallizes from water in anhydrous crystals. Its picrate melts a little higher than the melting-point given for cytosine picrate, but in other respects the salts are closely similar.

On the other hand, 2-oxy-6-aminopyrimidine crystallizes with 1 molecule of water of crystallization, like cytosine, and its properties agree in practically every respect, as far as can be judged, with the descriptions of the natural substance. The picrate, when prepared from the pure base, has a higher decomposing-point than that given for the picrate from natural cytosine. However, we are inclined to believe that our base and cytosine are identical and, therefore, the structure of cytosine is to be represented by formula I.¹ It will be necessary to compare our material with the natural before this can be definitely settled, and we hope soon to obtain a sample of the natural substance.

When 2-oxy-6-aminopyrimidine was heated with 20 per cent sulphuric acid for 3 hours at 150°-170° it was found that 15 per cent of the material was converted into uracil. Dr. Osborne informs us that to obtain uracil it was necessary to heat triticonucleic acid with acids for a considerable time.²

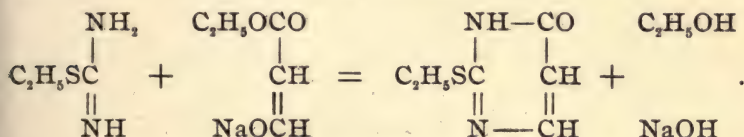
Since uracil results from the cleavage-cytosine, the natural

¹ The substance can naturally be viewed as 2-oxy-4-aminopyrimidine, and, on account of the usual nomenclature, this aspect better illustrates its character as a sort of hydrated fragment of uric acid. Its relation to uracil, however, is better shown by representing the substance as a 6-amino derivative or the tautomeric 6-imino form.

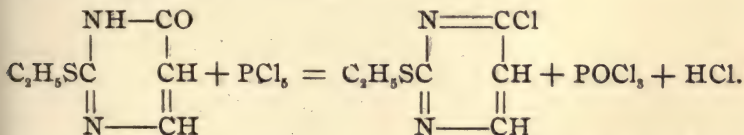
² See Report Conn. Agr. Expt. Sta. for 1901 p. 409.

assumption is that the analogous thymine, which until recently has been more widely obtained as a cleavage-product, results from the decomposition of a corresponding base, the as yet undiscovered 5-methylcytosine, this base undergoing cleavage more readily than cytosine. We intend to give an account of this new base later, the preparation of these bases being one of the first steps toward the synthesis of the nucleic acids.

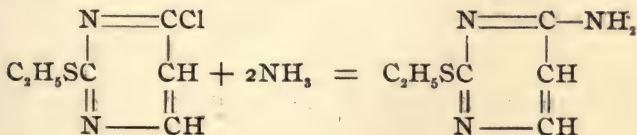
We prepared the synthetic cytosine as follows: The ethyl bromide addition-product of thiourea was treated with 1 molecule of alkali in aqueous solution and the sodium salt of ethyl formylacetate added. On standing a number of hours, then warming for a few minutes, cooling, and acidifying with acetic acid, 2-ethylmercapto-6-oxypyrimidine was obtained:



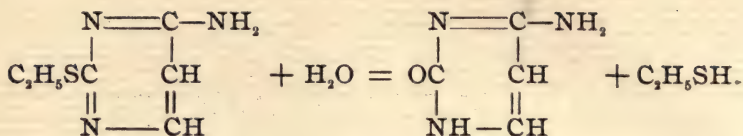
The 2-ethylmercapto-6-oxypyrimidine was converted into 2-ethylmercapto-6-chlorpyrimidine by means of phosphorus pentachloride and the phosphorus oxychloride was removed by evaporation in a vacuum.



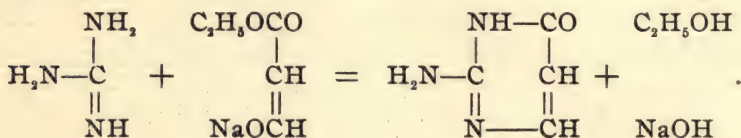
When 2-ethylmercapto-6-chlorpyrimidine was heated with alcoholic ammonia it gave 2-ethylmercapto-6-aminopyrimidine.



Finally the 2-ethylmercapto-6-aminopyrimidine was converted into the 2-oxy-6-aminopyrimidine by boiling with hydrobromic acid:

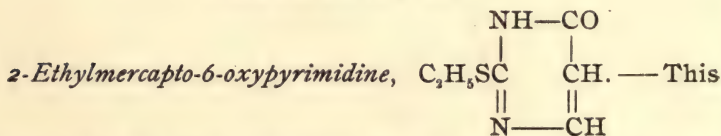


The synthesis of 2-amino-6-oxypyrimidine was effected by treating sodium formylacetic ester with free guanidine in aqueous solution, whereupon the following condensation took place :

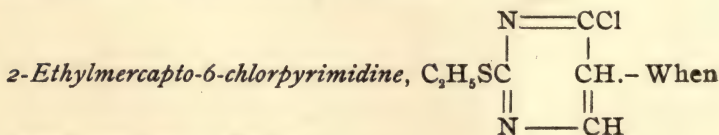


Sodium formylacetic ester is easily prepared by treating equal weights of ethyl formate and ethyl acetate, in two volumes of ether, with metallic sodium, according to the directions of Wislicenus.¹

EXPERIMENTAL PART.



compound has been described in the preceding article by Wheeler and Merriam. We have usually taken 50 grams of the ethyl bromide addition-product of thiourea,² dissolved in 10 per cent sodium hydrate, and have then added somewhat over the calculated quantity of dry sodium ethyl formylacetate. After standing for two or three hours the solution, heated to boiling and then cooled, was acidified with acetic acid. A yield of about 48 per cent of the calculated of crude mercaptooxypyrimidine was usually obtained.



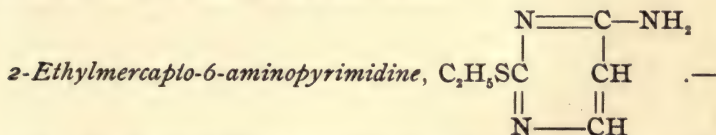
¹ Ber. d. chem. Ges., 20, 2933 (1887).

² Claus : Ann. Chem. (Liebig), 179, 145.

2-ethylmercapto-6-oxypyrimidine (5.3 grams) and phosphorus pentachloride (7.5 grams) were warmed on the steam-bath they reacted smoothly and hydrogen chloride was given off. The product was an oil. An attempt to purify it by distilling off the phosphorus oxychloride at ordinary pressure in an oil-bath, at 150° , caused decomposition. It was found that the oil could be distilled in steam, but the greater part was converted into uracil by this treatment. The portion purified in this manner (2 grams) was analyzed with the following result :

	Calculated for $C_6H_7N_3SCl$.	Found.
N	16.04	16.8

The oil, when dry, is stable at 150° . When boiled with hydrochloric acid it gives uracil. The chlorpyrimidine, for conversion into the amino derivative, was prepared as follows : 6.3 grams of 2-ethylmercapto-6-oxypyrimidine and 8.5 grams of phosphorus pentachloride were heated on the steam-bath until the action was complete. The phosphorus oxychloride was removed by heating in an oil-bath at 140° , under a pressure of 12 mm., for about fifteen minutes. The crude oil thus obtained weighed 6.5 grams, a yield of 92 per cent of the calculated. In another preparation 15.5 grams of the 2-ethylmercapto-6-oxypyrimidine gave 15.5 grams of chlorine compound, or 90 per cent of the calculated.

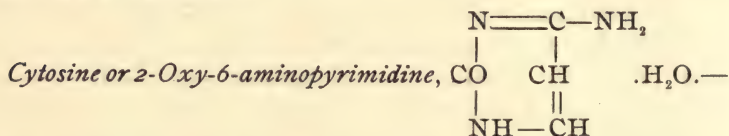


When 2-ethylmercapto-6-chlorpyrimidine (6.5 grams) was heated in a closed tube with alcoholic ammonia at 140° to 150° , for six hours, the action was complete. An odor of mercaptan was apparent on opening the tube, showing too energetic treatment, and ammonium chloride had separated. The alcohol was removed by evaporation, after filtering from ammonium chloride, and the dark varnish which was obtained was washed with a few cubic centimeters of cold water. By this treatment the material completely solidified to a hard

cake. It was very soluble in alcohol and in benzene, and fairly soluble in hot water. The weight of the crude product was 4.7 grams, a yield of 82 per cent of the calculated. The base dissolved immediately in dilute hydrochloric acid and was precipitated by ammonia in stout tables. It was purified by boiling in alcohol with animal charcoal and then crystallizing from 50 per cent alcohol. It separated in the form of colorless plates and melted at 85° to 86°. A nitrogen determination gave :

	Calculated for $C_6H_9N_3S$.	Found.
N	27.1	27.6

In another preparation the chlorpyrimidine was heated with alcoholic ammonia at 115° to 120° for five and a half hours. From 15.5 grams of the chlorine compound 11.6 grams of the base were obtained, which is a yield of 84 per cent of the calculated.



The above 2-ethylmercapto-6-aminopyrimidine (3 grams) was boiled with hydrobromic acid of boiling-point 125° (15 cc.) for two hours, when mercaptan had ceased being evolved. On evaporating the free hydrobromic acid on the steam-bath a beautiful crystalline mass of the hydrobromide was obtained. It crystallizes in the form of glistening prisms from a little water. The free base was obtained by dissolving the hydrobromide in water and precipitating with ammonia. The weight of the crude base was 1.9 grams, which is a yield of 79 per cent of the calculated. In another experiment 7.5 grams of 2-ethylmercapto-6-aminopyrimidine gave 5.6 grams of 2-oxy-6-aminopyrimidine, or 90 per cent of the calculated. The base for analysis was boiled with animal charcoal and crystallized from water. It was dried in the air and the water of crystallization determined by heating in an oven at 100° to 110°.

0.5166 gram substance lost 0.0727 gram on heating.

	Calculated for $C_4H_5ON_3 \cdot H_2O$.	Found.
H_2O	13.95	14.07

The analysis of the dried material gave the following results :

0.2188 gram substance gave 0.3498 gram CO_2 and 0.0835 gram H_2O .

0.0939 gram substance gave 31 cc. moist N at 25° and 773 mm. pressure.

	Calculated for $C_4H_5ON_3$.	Found.
C	43.25	43.60
H	4.50	4.25
N	37.84	37.72

Properties of 2-Oxy-6-aminopyrimidine.—The free base, when first obtained, crystallized from hot water in the form of needle-like prisms. It was then somewhat colored (pale brownish), and melted, or rather decomposed, at 320° to 325° with violent effervescence, first becoming dark-colored a little below 300° . After boiling in aqueous solution with animal charcoal it crystallized in the form of beautiful, colorless, transparent plates. The edge of one of these crystals, which perhaps was made up of a number of plates, measured three-quarters of an inch in length. The faces were so badly etched, or striated, or covered with vicinal growths, that crystallographic measurements were impossible. They probably belong to the mono- or triclinic system. The plates had the same effervescing-point on heating as the needle-like prisms. These decomposing-points were taken in capillary tubes, in a paraffin-bath, on an Anschütz thermometer 13.5 centimeters in length, and are uncorrected. The plates dissolve in about 129 parts of water at 25° . The base is precipitated by phosphotungstic acid. It would, therefore, be found in the histidine fraction. When the acidified solution is treated with potassium bismuth iodide it gives a brick-red precipitate. It gives the murexide reaction. With sulphuric and hydrochloric acids it gives readily soluble salts. The chloroplatinate, and especially the picrate, are difficultly soluble in water. The gold double salt is also not very soluble. Kossel and Steudel give

no melting- or decomposing-point for their cytosine, but state that the picrate turned brown on heating to 255° and melted at 270° with decomposition.

2-Oxy-6-aminopyrimidine Picrate.—Picric acid produced an immediate precipitate, which crystallized in bright-yellow needles or very slender, needle-like prisms. When made from material that had not been decolorized with animal charcoal, and therefore containing a slight impurity, it decomposed with violent effervescence quite sharply at about 264° . When prepared from the pure oxyaminopyrimidine the crystals had a more pronounced prismatic habit and they showed no melting-point, but sintered, became black, and decomposed at about 300° to 305° . One hundred parts of water dissolve 0.076 parts of the salt at 25° . Our experience with these picrates has shown that the melting-points are rather indefinite. They can be made to effervesce at a somewhat higher or lower temperature, according to the rate of heating. They are difficult to analyze on account of the ease with which oxides of nitrogen pass over. A nitrogen determination of a sample prepared from the pure base, for example, gave :

	Calculated for $C_4H_5ON_3 \cdot C_6H_3(NO_2)_3OH$.	Found.
N	24.7	26.4

The *chloroplatinate* separates as a precipitate in yellow flakes. A platinum determination gave :

	Calculated for $(C_4H_5ON_3)_2H_2PtCl_6$.	Found.
Pt	30.83	30.60

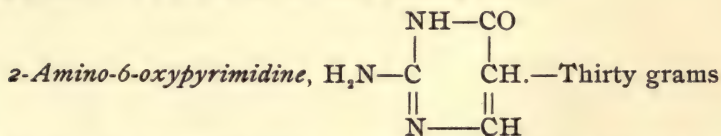
2-Oxy-6-acetaminopyrimidine was prepared by heating 0.5 gram of the amino derivative with acetic anhydride. It proved to be practically insoluble in alcohol and difficultly soluble in water. It crystallized from hot water in colorless, microscopic prisms, with rough faces, frequently occurring in crosses. It showed no signs of melting at 300° . A nitrogen determination gave :

	Calculated for $C_6H_7O_2N_3$.	Found.
N	27.44	27.82

The *phenyl isocyanate derivative* was prepared by heating 0.5 gram of the base with 0.55 gram of phenylisocyanate on the steam-bath for six hours. The white crystalline product which resulted proved to be very insoluble. It was boiled repeatedly with alcohol and then digested with water. The insoluble material thus obtained began to sinter on heating at about 255°, and then melted with violent effervescence at 260°. A nitrogen determination agreed with the calculated for an addition of 2 molecules of phenyl isocyanate to one of the base.

N	Calculated for		Found.
	(1 : 1) C ₁₁ H ₁₀ O ₂ N ₄ .	(2 : 1) C ₁₈ H ₁₆ O ₂ N ₅ .	
	24.34	20.05	20.4

Action of Bromine.—Three-tenths gram of 2-oxy-6-aminopyrimidine was treated with 1 gram of glacial acetic acid, and 0.5 gram of bromine was added. An immediate reaction took place, heat was evolved, and an orange powder separated, which dissolved on warming. Some water was added to the cooled solution and the precipitate produced was crystallized from water. It formed well-crystallized, colorless needles, and it melted sharply at 247° with effervescence. When dissolved in water and made alkaline with ammonia it gave a strong, wine-red color, and, on cooling, a brick-red substance separated. This had no definite melting-point.



of guanidine carbonate were dissolved in 100 cc. of water and mixed with 54 grams of crystallized barium hydrate in 400 cc. of water. The solution was filtered and 55 grams of sodium ethyl formylacetate were added. The whole dissolved except a slight sediment. After standing for three hours the solution was divided into two equal portions. One was allowed to stand over night, the other was warmed on the steam-bath for a few minutes, and then just acidified with sulphuric acid. The filtered solution on evaporation, and adding ammonia in excess, gave a crystalline, brown precipitate, weigh-

ing 6.7 grams, or 36 per cent of the calculated. The portion that stood over night, on similar treatment, gave practically the same yield, so that long standing does not better the yield. In another experiment 10 grams of guanidine carbonate and 22 grams of sodium ethyl formylacetate gave 4.8 grams of the base, which is a yield of 39 per cent of the calculated. On boiling the crude products with animal charcoal, in aqueous solution, the color is slowly removed and, on cooling, small, flat, colorless, transparent prisms generally separate. These crystals, when air-dried, contained less than 0.5 per cent of water. A nitrogen determination (I.) gave:

I. 0.0900 gram substance gave 30.6 cc. of moist N at 26°.5 and 762 mm. pressure.

II. 0.1357 gram substance gave 44.8 cc. of moist N at 24° and 768 mm. pressure.

	Calculated for $C_4H_6ON_3$.	I.	Found. II.
N	37.83	37.98	37.45

In another experiment, as above, the base was crystallized from water, purified with animal charcoal, and when a portion had separated from the still warm solution, in the form of prisms, the mother-liquor was decanted. It then became almost semi-solid from the separation of a mass of long, slender, colorless, silky needles which, on drying in the air, formed a bulky, felt-like mass. This material contained, or occluded, water, but the determinations were not constant: 0.8567 gram substance lost 0.1036 gram on heating to 100° to 110°, equivalent to 12.0 per cent water. The needle form appears to result also from dilute solutions or on rapidly cooling. 2.0527 grams of substance prepared in this manner, on standing in the air for eight or nine hours and then heating, lost 0.1657 gram, equal to 8.7 per cent of water. The calculated for 1 molecule of water is 13.9 per cent. A nitrogen determination of the dried material is given above (Analysis II.).

Properties of 2-Amino-6-oxypyrimidine.—It was found that the needles gave the stout prisms and the prisms could be obtained in needle form under slight changes in the crystallization. The crystals were not suitable for crystallographic

measurements, the faces being highly etched, especially the end faces of the prisms. The material melts, or rather decomposes, with violent effervescence, at about 276° . This effervescing-point may vary several degrees, according to the rate of heating.

The base is precipitated by phosphotungstic acid. It is not precipitated by potassium bismuth iodide in hydrochloric acid solution, but it gives a brick-red precipitate in solutions of the base in sulphuric acid. It gives the murexide reaction. Its sulphate and hydrochloride are readily soluble in water and the former crystallizes in flat prisms. The picrate is very difficultly soluble and the gold and platinum double salts are also not very soluble. When heated with 20 per cent sulphuric acid for two hours, at 145° to 150° , a portion of the material is converted into uracil.

2-Amino-6-oxypyrimidine Picrate.—When picric acid is added to a hot solution of the base in water a mass of bright-yellow needles separate. If slowly cooled slender prisms are formed. On heating, the crystals become less transparent at about 180° , showing evidence of darkening at about 255° , and signs of melting at 270° . Between this point and 280° they generally effervesce. They dissolve in about 1200 to 1300 parts of water at 25° . A nitrogen determination gave :

	Calculated for $C_4H_5ON_3 \cdot C_6H_2(NO_2)_3OH$.	Found.
N	24.70	24.72

The *chloroplatinate* separates in the form of small yellow needles, which form acicular crystals or spikes on slowly cooling the hot solutions. On heating, it decomposes above 200° , becoming brown, but not melting below 286° . A platinum determination gave :

	Calculated for $(C_4H_5ON_3)_2H_2PtCl_6$.	Found.
Pt(=194.8)	30.83	30.56

The *gold chloride double salt*, which seems to be more soluble than the platinum double salt, forms bright-yellow, stout prisms, which easily form a supersaturated solution. A gold determination gave :

	Calculated for $C_4H_5ON_3 \cdot HCl \cdot AuCl_3$.	Found.
Au(=195.7)	43.51	43.57

2-Acetamino-6-oxypyrimidine.—One-half gram of the base required about 7.5 grams of boiling acetic anhydride to effect solution. On cooling, a colorless mass of crystals separated, so bulky that the test-tube could be inverted without loss of the contents. This material crystallizes in bunches of minute mother-of-pearl scales from alcohol, and it melts at 247° to a clear liquid. A nitrogen determination gave:

	Calculated for $C_6H_7O_2N_3$.	Found.
N	27.45	27.69

2-Amino-5-brom-6-oxypyrimidine.—Three grams of the base were suspended in 20 cc. of glacial acetic acid, in which it is difficultly soluble, and 4.5 grams of bromine were dropped in. The action took place smoothly and an orange powder separated. It weighed 6.6 grams, while the calculated amount for a hydrobromide of 2-amino-5-brom-6-oxypyrimidine is 7.2 grams. The yield obtained was 83 per cent of the theoretical. This hydrobromic acid salt forms long, slender, needle-like prisms, when crystallized from water, and it melts at about 273° with strong effervescence. When the aqueous solution of this is treated with ammonia the brom-base separates as a compact, granular precipitate, insoluble in alcohol and extremely difficultly soluble in water. It crystallizes from strong acetic acid in radiating masses of pointed plates, and it melts with decomposition at about the same temperature as the hydrobromide or the bromine-free base. It has acid properties and it dissolves in strong ammonia, but separates again unaltered on boiling off the ammonia. A nitrogen determination gave:

	Calculated for $C_4H_4ON_3Br$.	Found.
N	22.10	22.13

Contributions from the Sheffield Laboratory of Yale University.

CIV.—ON CYTOSINE OR 2-OXY-6-AMINOPYRIMIDINE FROM TRITICO-NUCLEIC ACID.

BY HENRY L. WHEELER AND TREAT B. JOHNSON.

It has been shown by Osborne and Harris¹ that uracil can be obtained from the nucleic acid of the wheat embryo.² As we wished to compare our synthetic uracil with some of the natural we asked Dr. Osborne for a sample. Not having the pure substance at hand, he very kindly supplied us with 1.35 grams of material obtained by evaporating the mother-liquors from the crystallization of his uracil.

We found that the material, after crystallizing six times from water, gave a solution which, on slowly evaporating, deposited flat, needle-like crystals, about a centimeter in length. This material was obviously not uracil, and, at Dr. Osborne's suggestion, we then examined the material for cytosine. We found, in fact, that it consisted of a mixture of apparently about equal parts of uracil and cytosine.

When a solution of 3 grams of picric acid, dissolved in 200 cc. of hot water, was added to the 1.35 grams of material dissolved in 50 cc. of hot water and the mixture was allowed to stand for twelve hours, beautiful, long, silky, bright-yellow needles separated. The weight of the picrate obtained was 1.7 grams. The needles, which had every appearance of purity, melted with effervescence, as Kossel and Steudel³ state in the case of thymus cytosine at about 270°, turning brown a number of degrees below this temperature.⁴ We took exactly 1 gram of this picrate for the preparation of the free base. The picrate was treated with an excess of sulphuric acid and

¹ Ztschr. physiol. Chem., 36, 85; Annual Report for 1901 of the Connecticut Agricultural Experiment Station, page 408.

Osborne and Campbell: J. Am. Chem. Soc., 22, 379.

³ Ztschr. physiol. Chem., 37, 378 (1903).

⁴ Owing to the ease with which this picrate gives off oxides of nitrogen, the analytical results came high both for carbon and nitrogen, so that the results were without value. In this connection it may be stated that a nitrogen determination gave 26.5 per cent nitrogen, while a precisely similar result was obtained in the case of the picrate from the synthetic base, namely 26.4 per cent nitrogen. The calculated for $C_4H_5ON_3 \cdot C_6H_3(NO_2)_3OH$ is 24.7 per cent nitrogen.

the picric acid was removed by shaking with ether. The sulphuric acid was mostly removed by barium hydrate, and, on concentrating and adding ammonia, colorless, well-crystallized, slender, needle-like prisms of the free base separated. The amount of this material was 0.1641 gram. This, after washing with water, was dried by standing in the air, on paper, for twelve hours. It then lost 0.0181 gram on heating to constant weight at 110° to 120°, equivalent to 11.30 per cent of water, while the calculated for $C_4H_5ON_3 \cdot H_2O$ is 13.9 per cent water.

This base melted with strong effervescence at about 323°, precisely like the synthetical 2-oxy-6-aminopyrimidine, and when a portion was mixed with the latter substance the melting- or effervescing-point was not lowered.

After determining the solubility in water (see below) the base was then converted into the chloroplatinate. A platinum determination gave :

0.0830 gram substance gave 0.0253 gram platinum.

	Calculated for ($C_4H_5ON_3$) ₂ H ₂ PtCl ₆ .	Found.
Pt(=194.8)	30.83	30.48

The remaining material was given to Professor S. L. Penfield for a crystallographic examination and comparison with the corresponding platinum double salt prepared from 2-oxy-6-aminopyrimidine. Kossel and Steudel¹ state, in regard to the platinum chloride double salts prepared by them, that "Das Platindoppelsalz des Störcytosins zeigte nämlich fast durchweg doppelbrechende Zwillingsformen, welche in der Weise aneinander gelagert waren, dass die Auslöschungsrichtung in dem einen Krystall einen Winkel von 53° mit der Auslöschungsrichtung des anderen Krystalls bildete. Diese Winkel wurden beim Cytosin aus Herings- und Störtestikeln gleich befunden, beim Cytosin aus Thymusnucleinsäure haben wir bisher solche Zwillingsformen überhaupt nicht beobachtet."

¹ Ztschr. physiol. Chem., 37, 379 (1903).

Crystallography of 2-Oxy-6-aminopyrimidine Chloroplatinate
(*Synthetic Cytosine Chloroplatinate*).

The crystals submitted for study were thin plates and for examination with the microscope they were embedded in oil, and over them a cover glass was placed.

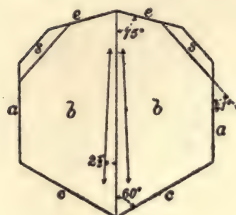


Fig. I.

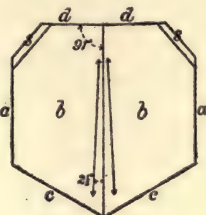


Fig. II.

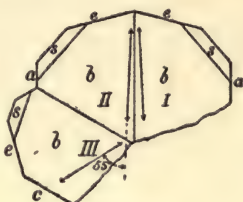


Fig. III.

Figure I. represents the habit of one of the crystals which was unbroken and of almost ideal symmetry. It is a twin, presumably belonging to the monoclinic system, the large flat face b being the clinopinacoid (010). The edges c , a , and e appear as sharp lines under the microscope, and represent the direction of faces at right angles to b . It may be assumed that c is the base (001) and a the orthopinacoid (100), the inclination of the axes, β , being about 60° . Some beveling form, s , appears at the upper corners, which may be taken as the monoclinic pyramid ($\bar{1}11$), its intersection with b making an angle of about 41° with the vertical axis (the trace of a), as indicated in the figure. The faces e at the top are orthodomes, inclined about 75° to the vertical axis, and they have the symbol ($\bar{1}02$). The twinning plane, uniting the two individuals, is the orthopinacoid a . The extinction, indicated in the figure by the arrows, is inclined about $2^\circ.5$ either side of the twinning plane.

A second crystal, Fig. II., was like the one just described, except for the faces d at the top, which make an angle of about 91° with the vertical axis. The form d is evidently an orthodome, and has the symbol ($\bar{1}03$).

A third crystal, Fig. III., showed two kinds of twinning. Crystals I. and II. are twinned about the orthopinacoid as in

Fig. I., while II. and III. have the base c as the twinning plane. The extinction is indicated by the arrows. In crystals II. and III. the extinction directions make an angle of 55° with one another.

Crystallography of Wheat Cytosine Chloroplatinate.

The crystals submitted for study were much thinner than those prepared from synthetic cytosine, hence when mounted in oil for examination they were much more broken.

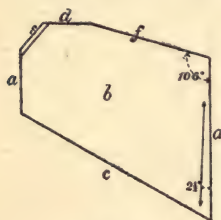


Fig. IV.

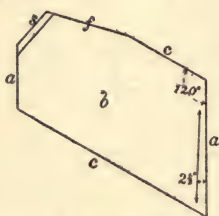


Fig. V.

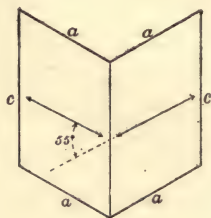


Fig. VI.

Fig. IV. represents a fragment of a twin crystal, the part to the right of the twinning plane not being shown. The arrangement of the faces and the angles is like Fig. II., except f , at the top, which makes an angle of 106° with the vertical axis and corresponds to an orthodome ($\bar{1}06$).

Fig. V. represents a part of another twin crystal, like Fig. IV., except that f and c terminate the crystal instead of d and f . The extinction was $2^\circ.5$ from the vertical axis as in the case of the synthetic preparation.

Among the broken fragments two kinds of twinning were observed, some with a as the twinning plane and others like Fig. VI., with the base c as the twinning plane. In the latter the twinning law is the same as that of crystals II. and III. of Fig. III. The extinction is nearly parallel to a , and makes an angle with the twinning plane of $62^\circ.5$, or the two extinction directions make an angle of 55° with one another.

Aside from the extinction directions the optical properties of the crystals were not very decisive. When examined in convergent light an indistinct interference figure was seen, presumably the center of the cross of an obtuse bisectrix.

The identity of the synthetic cytosine and wheat cytosine is established beyond question by the crystallographic similarity of the two chloroplatinates.

The measurements given were made under the microscope, and only approximate accuracy is claimed for them. The symbols of the domes e ($\bar{1}02$), d ($\bar{1}03$), and f ($\bar{1}06$) were determined by plotting.

Dr. P. A. Levene has very kindly sent us a pure sample of his base from the spleen which has the properties and composition of Kossel and Steudel's cytosine. The amount of this at our disposal was about 0.12 gram. It formed thin, flat, colorless crystals or prismatic plates, and it melted or effervesced, side by side with the synthetic material at 323° , and, when portions of these substances were mixed, the melting-point was not altered in the slightest. After determining the solubility we converted this material into the chloroplatinate. Professor Penfield then reported on the crystallography as follows :

Crystallography of Spleen Cytosine Chloroplatinate.

The crystals are like the ones previously described, having the same angles, though presenting some variation in habit. Fig. VII. is typical, showing a , b , c , and s forms, but with

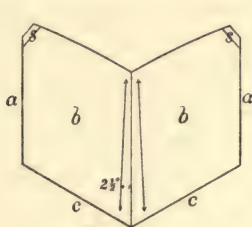


Fig. VII.

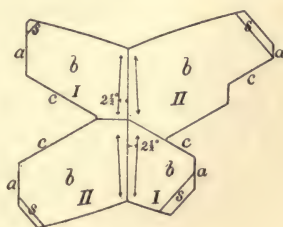


Fig. VIII.

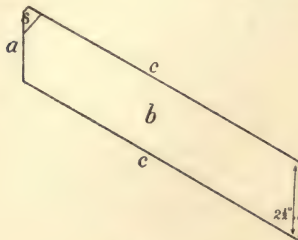


Fig. IX.

the reentrant angle at the top having a curved contour so that no definite symbol can be assigned. The extinction, as in the other preparations, is $2^{\circ}.5$ either side of the twinning plane, as indicated by the arrows in the figure.

Fig. VIII. represents a penetration twin, drawn with camera lucida. The two opposite parts I. and I. extinguish simultaneously, as also II. and II. Many crystals of the crop submitted for examination were long, lath-shaped individuals, Fig. IX. Several having this habit were twinned about the *c* face.

The three chloroplatinates prepared from synthetic cytosine, wheat cytosine, and spleen cytosine are crystallographically identical and show no greater variation in habit than is generally observed on crystals of any substance formed under varying conditions.

The solubility of the three samples of cytosine in water at 25° was determined with the following results :

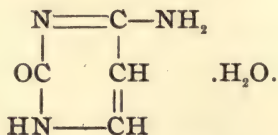
100 parts water dissolve 0.83 part wheat cytosine.

100 parts water dissolve 0.78 part spleen cytosine.

100 parts water dissolve 0.79 part synthetic cytosine.

The high result in the case of wheat cytosine is probably due to the fact that it was not as pure as the others. Owing to lack of material the determination was made with the above-mentioned sample, which had been washed but not recrystallized from water.

We conclude, from these results, that the products obtained from the three different sources are identical, and that cytosine, is as Kossel and Steudel have predicted, an oxyamino-pyrimidine, *viz.*, 2-oxy-6-aminopyrimidine. Its structure is to be represented by the following formula, or a tautomeric form :



Hitherto cytosine has been found only in animal organs. The present results offer further evidence of the similarity of nucleic acids of animal and vegetable origin.

We take pleasure in thanking Dr. Osborne and Dr. Levene for the material placed at our disposal and Professor Penfield for the crystallographic descriptions.

NEW HAVEN, CONN., March 25, 1903.

[Reprinted from the American Chemical Journal, Vol. XXXI, No. 6.
June, 1904.]

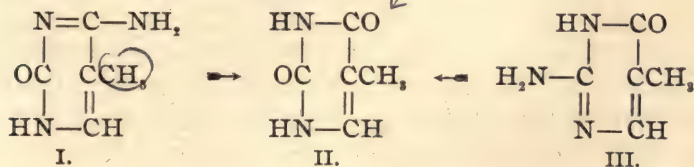
Contributions from the Sheffield Laboratory of Yale University.

CXVI.—RESEARCHES ON PYRIMIDINE DERIVATIVES: 5-METHYLCYTOSINE.

[FIFTH PAPER.]

BY HENRY L. WHEELER AND TREAT B. JOHNSON.

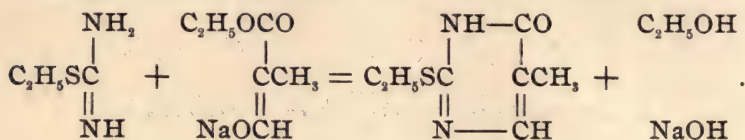
In a previous paper we¹ showed that cytosine gives uracil on heating with acids. If uracil is to be reckoned as cytosine in the nucleic acids then 5-methyluracil or thymine possibly results by the cleavage of a corresponding base, namely, 5-methylcytosine (formula I.) or the isomeric 2-amino-5-methyl-6-oxypyrimidine (III.):



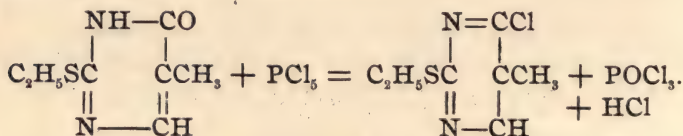
We therefore decided to prepare these new bases and to compare their properties with those of cytosine. In this paper we describe 5-methylcytosine and in a later paper by Dr. Johnson and Mr. S. H. Clapp, the compound represented by formula III. will be discussed. We prepared the compound represented by formula I. as follows: The ethyl bromide addition-product of thiourea was treated with one molecular

¹ This JOURNAL, 29, 494 (1903).

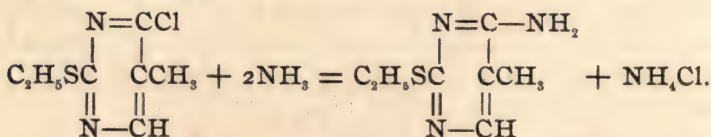
proportion of alkali in aqueous solution and the sodium salt of ethyl formylpropionate added. On standing, then warming for a few minutes, cooling, and acidifying with acetic acid, 2-ethylmercapto-5-methyl-6-oxypyrimidine was obtained.



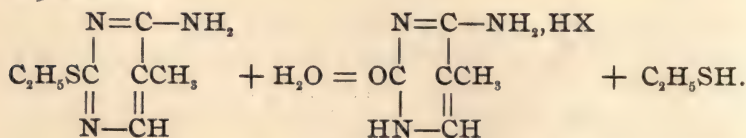
The 2-ethylmercapto-5-methyl-6-oxypyrimidine was converted into 2-ethylmercapto-5-methyl-6-chlorpyrimidine by means of phosphorus pentachloride :



When 2-ethylmercapto-5-methyl-6-chlorpyrimidine was heated with strong alcoholic ammonia it gave 2-ethylmercapto-5-methyl-6-aminopyrimidine.



Finally the 2-ethylmercapto-5-methyl-6-aminopyrimidine was converted into the halogen hydride salt of 2-oxy-5-methyl-6-aminopyrimidine by boiling with either hydrochloric or hydrobromic acid.



5-Methylcytosine separates from water with a half molecule of water of crystallization while cytosine crystallizes with 1 molecule of water.

5-Methylcytosine is about five times as soluble in water as cytosine and ten or eleven times as soluble as thymine or uracil and it is readily decomposed into thymine by 20 per cent sulphuric acid at 150°. It is probable that in the decomposition of the nucleic acids by the prolonged action of hot acids this base would, if present, be converted entirely into thymine.

One of the most characteristic properties of 5-methylcytosine is its tendency to form the so-called abnormal or basic 2 : 1 salts with hydrochloric and hydrobromic acids. When ammonia in excess is added to a solution of cytosine in these acids, free cytosine usually separates. In the case of 5-methylcytosine in the halogen hydride acids the precipitate generally consists of the salt $(C_5H_7ON_3)_2HX \cdot H_2O$.

Cytosine gives a 1 : 2 salt with concentrated hydrochloric acid; 5-methylcytosine gives a 1 : 1 salt under the same conditions.

The picrate of 5-methylcytosine, which forms yellow, long, slender, needle-like prisms, has the same solubility in water as cytosine picrate.

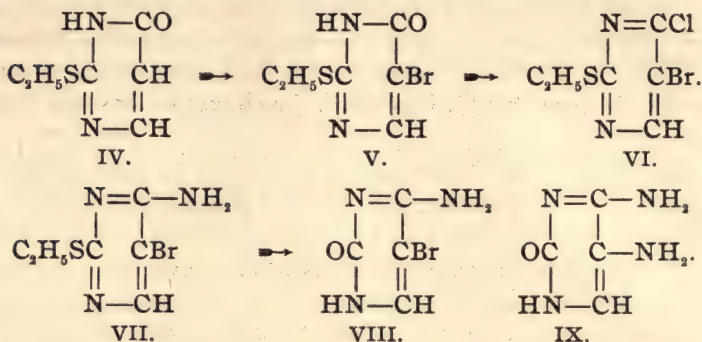
5-Methylcytosine is precipitated by phosphotungstic acid; it therefore differs from the new base prepared by Kutscher¹ from thymus nucleic acid.

An attempt was made to prepare 2-oxy-5,6-diaminopyrimidine by brominating 2-ethylmercapto-6-oxypyrimidine² (IV.), chlorinating in the 6-position by means of phosphorus pentachloride, and then attempting to replace both of the halogens by the amino group in this compound (VI.) by means of alcoholic ammonia at a high temperature. It was found that the chlorine could be replaced by the amino group with ease, but that the bromine was far more firmly bound, the compound VII. being almost quantitatively obtained. This was converted into 5-bromcytosine (VIII.) and this compound then heated with aqueous ammonia, but here again the desired diamino derivative was not obtained. These results recall the similar behavior of 4-methyl-6-amino-5-brompyrimidine de-

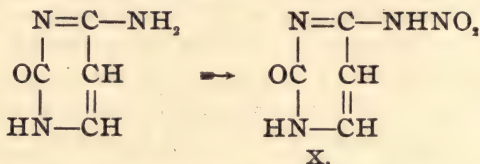
¹ Ztschr. physiol. Chem., **38**, 173 (1903).

² Wheeler and Merriam : This JOURNAL, **29**, 484 (1903).

scribed by Gabriel and Colman.¹ This substance did not react with ammonia without complete decomposition.



The action of nitric acid was next tried on cytosine, whereupon it was found that nitration took place; the compound formed was not a 5-nitro derivative, but rather the nitramide whose structure is, in all probability, shown by formula X.



The formation of similar nitramide derivatives in the pyrimidine series has been observed by Gabriel and Colman.²

Work on the preparation of oxydiaminopyrimidines will be continued here. These particular pyrimidine compounds are of special interest not only because Kutscher³ believes that he has isolated such a compound, in the form of its picrate, from yeast, but also on account of the fact that if an oxydiaminopyrimidine is found to crystallize or combine with 3 molecules of water it would then have the same percentage composition as Drechsel's so-called diaminoacetic acid⁴ and perhaps the substances would prove to be identical. Willstätter⁵ has shown that diaminoacetic acid, if capable of ex-

¹ Ber. d. chem. Ges., **34**, 1239 (1901).

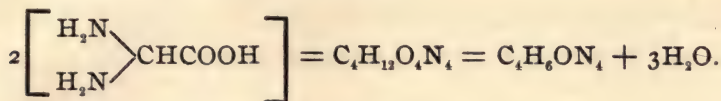
² *Ibid.*, **34**, 1240-1241 (1901).

³ Ztschr. physiol. Chem., **38**, 176 (1903).

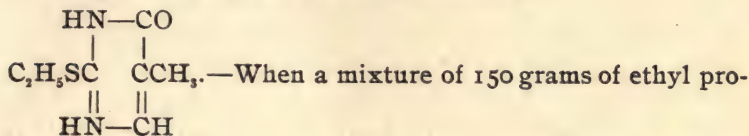
⁴ Beilstein: Handbuch I., 1194.

⁵ Ber. d. chem. Ges., **35**, 1378 (1902).

istence, would not agree in properties with Drechsel's compound. In other words, Drechsel's compound might be a pyrimidine derivative as follows :



EXPERIMENTAL PART.

2-Ethylmercapto-5-methyl-6-oxypyrimidine,

pionate and 135 grams of ethyl formate, in somewhat over 2 volumes of dry ether, were slowly dropped upon 34 grams of sodium, about 125 grams of crude sodium ethylformylpropionate¹ were obtained. In using this salt and also sodium ethylformyl acetate to condense with the alkyl halide addition-products of thiourea we² employed the substances in molecular proportions. It has since been found in both cases that only about one-half, or less, of the quantity of the salt taken reacts in the desired manner, and therefore that one-half the calculated quantity of pseudoethylthiourea hydrobromide gives about the same, if not a better, yield of pyrimidine as when the substances are used in molecular proportions. From 125 grams of the salt and 150 grams of the ethyl bromide addition-product of thiourea we obtained, in the manner already described, 39.5 grams of this mercaptopyrimidine. This is 28 per cent of the calculated. In another experiment 90 grams of the sodium salt with 87 grams of the thiourea addition-product gave 20.5 grams of the pyrimidine derivative, or 26 per cent of the theoretical amount.

2-Ethylmercapto-5-methyl-6-oxypyrimidine crystallizes from hot water in the form of long, slender prisms. It is very sol-

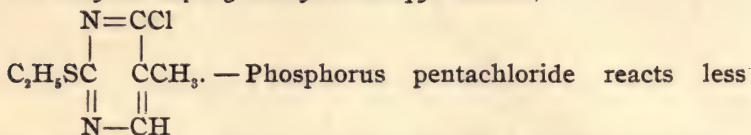
¹ Wislicenus: Ber. d. chem. Ges., 20, 2933 (1887).

² This JOURNAL, 29, 487; *Ibid.*, 29, 496 (1903).

uble in alcohol and it melts at 158° to 159° . A nitrogen determination gave :

	Calculated for $C_7H_{10}ON_2S$.	Found.
N	16.47	16.78

2-Ethylmercapto-5-methyl-6-chlorpyrimidine,



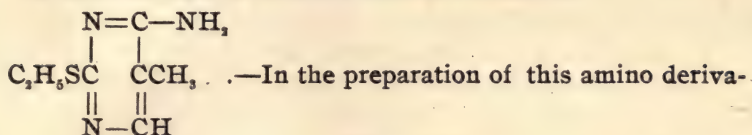
smoothly with the above mercapto derivative than it does with 2-ethylmercapto-6-oxypyrimidine. When the mixture of the substances in molecular proportions is warmed on the steam-bath, hydrogen chloride is evolved, and, on cooling, the material solidifies to a deliquescent, crystalline cake. This is apparently a double compound of the chlorpyrimidine and phosphorus oxychloride. If an attempt is made to distil this directly in a vacuum, decomposition takes place and the material turns black. If, however, the cake is transferred to crushed ice it liquefies, and on shaking out with ether and drying, the resulting oil can then be distilled under diminished pressure. In one experiment, 35 grams of the mercapto-oxy derivative and 43.5 grams of phosphorus pentachloride gave 24 grams of the distilled chloride, which is a yield of 61.8 per cent of the calculated. In another, 20 grams gave 14.5 grams of the chloride or 65 per cent of the calculated.

2-Ethylmercapto-5-methyl-6-chlorpyrimidine boils at 146° to 147° at 17 mm. pressure, and at 157° to 159° at 25 to 26 mm. pressure. It was thus obtained as a colorless, almost odorless, oil, which did not solidify in a freezing-mixture.

2-Ethylmercapto-6-chlorpyrimidine, prepared and purified in a similar manner, was found to boil at 135° at 24 mm. pressure.

A nitrogen determination in the case of 2-ethylmercapto-5-methyl-6-chlorpyrimidine, boiling at 157° to 159° , gave :

	Calculated for $C_7H_9N_2SCl$.	Found.
N	14.85	15.00

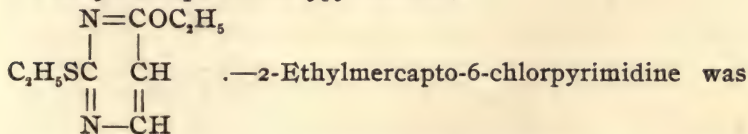
2-Ethylmercapto-5-methyl-6-aminopyrimidine,

tive, and also in the case of mercaptocytosine, the alcoholic ammonia used should be thoroughly saturated (in the cold), as otherwise an ethoxy derivative is formed instead of an amino compound.

We found that 13 grams of the above chloride and about 75 cc. of alcoholic ammonia, when heated for three hours at 127° , gave 10 grams of amino derivative, or 86.9 per cent of the calculated, and also that 10.1 grams of the chloride, when heated for two hours at 124° to 130° , gave 6.6 grams of the amino base after crystallizing from 50 per cent alcohol, or 74 per cent of the theoretical amount.

2-Ethylmercapto-5-methyl-6-aminopyrimidine is very soluble in alcohol and quite difficultly soluble in water. It crystallizes from 50 per cent alcohol in the form of colorless, small, stout, six-sided tables and prisms, which melt at 96° to 97° . It has a tendency to separate from its solutions as an oil, which finally crystallizes. A nitrogen determination gave :

	Calculated for $\text{C}_7\text{H}_{11}\text{N}_3\text{S}$.	Found.
N	24.86	25.20

2-Ethylmercapto-6-ethoxypyrimidine,

dissolved in alcohol and ammonia gas was passed in, the whole being heated on the steam-bath. After two hours, 7.5 grams of ammonium chloride had separated, the calculated quantity being 7.6 grams. On evaporating the alcoholic solution an oil was obtained which distilled at 137° to 138° at 18 mm.

pressure. A nitrogen determination agreed with the calculated for an ethoxy derivative :

	Calculated for $C_8H_{12}ON_2S$.	Found.
N	15.21	15.38

That this ethoxy derivative is not an intermediate product in the preparation of the amino compound was shown when on heating the oil with alcoholic ammonia for four or five hours at 150° to 175° it still remained unaltered.

This oil dissolves in dilute hydrochloric acid and is precipitated unaltered by ammonia. On boiling for several hours with strong acid it is converted quantitatively into uracil, melting at 338° . A nitrogen determination gave 25.4 per cent nitrogen, while the calculated is 25.0.

Cytosine Dihydrochloride.—When 2-ethylmercapto-6-amino-pyrimidine is warmed on the water-bath for three or four hours with concentrated hydrochloric acid, then cooled, beautiful, stout, brittle, colorless, flat prisms separate. The following analysis shows that this material is an acid salt :

	Calculated for $C_4H_5ON_3 \cdot 2HCl$.	Found.
Cl	38.58	39.09

This salt is analogous to the acid sulphate, $C_4H_5ON_3 \cdot H_2SO_4$, described by Kossel and Steudel.¹

5-Methylcytosine Monohydrochloride (Anhydrous).—When 2-ethylmercapto-5-methyl-6-aminopyrimidine was warmed with hydrochloric acid, in a similar manner to the above, mercaptan was evolved and the crystals obtained were colorless tables and flat prisms, which, when dried over potassium hydroxide, showed signs of melting at about 270° , and melted with effervescence at 288° . The material was readily soluble in water. A chlorine determination showed that this was an anhydrous 1 : 1 salt.

	Calculated for $C_5H_7ON_3 \cdot HCl$.	Found.
Cl	21.98	21.99

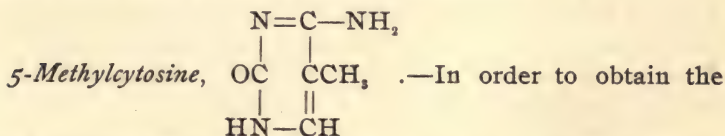
When 6.6 grams of the crude mercapto base were warmed

¹ Ztschr. physiol. Chem., 38, 53 (1903).

on the steam-bath with hydrochloric acid until mercaptan ceased being evolved, the solution evaporated to dryness, and the residue dissolved in a little water, 0.7 gram thymine was obtained, the formation of this being due to the presence of an ethoxy derivative. When this 1 : 1 hydrochloride was dissolved in water and to the warm solution an excess of ammonia was added, microscopic colorless needles slowly separated. These were not very soluble in hot water and difficultly in cold. The material was recrystallized from water. The curious result was then observed that the material still contained chlorine and that we had to deal with a basic salt or, more probably, a mixture of free base and a hydrous basic salt. The analytical results agreed fairly with the calculated for $(C_5H_7ON_2)_2HCl \cdot 3H_2O$.

	Calculated.	Found.
Cl	9.4	9.09
H ₂ O	7.1	7.53

The water determination was made by heating the material to constant weight at 150°. When the 1 : 1 hydrochloride is boiled with water a basic salt also is obtained.



free base the above material was dissolved in water, the chlorine was removed by means of silver sulphate, the excess of silver was precipitated with hydrogen sulphide and the sulphuric acid by barium hydrate, the excess of the latter by carbon dioxide. The clear, colorless solution was then concentrated to a small volume, whereupon, on cooling, beautiful, flat, colorless, prismatic, brittle crystals separated that formed a sandy powder. When heated, the crystals gave off water above 100° and showed signs of melting at 240°, melting with effervescence at 270°; this is 50° lower than the melting-point of cytosine.

100 parts of water dissolved 4.5 parts of the base at 25°.

2.387 gram substance lost 0.1544 gram on heating to constant weight at 135° to 145° (I.).

	Calculated for ($C_5H_7ON_3$) ₂ .H ₂ O.	I.	Found. II.
H ₂ O	6.71	6.46	6.30
	Calculated for $C_5H_7ON_3$.		Found.
N	33.60		33.44

Silver nitrate, added to an aqueous solution of this base, gives a gelatinous white precipitate soluble in an excess of ammonia and in nitric acid. The ammonia solution can be boiled without reduction.

Mercuric chloride gives a white precipitate in dilute solutions of the base; this dissolves on heating and separates again, on cooling, possibly in crystalline form.

Phosphotungstic acid gives a white precipitate insoluble in dilute hydrochloric or sulphuric acids.

5-Methylcytosine Monohydrochloride (Hydrous).—An attempt was made to prepare a dihydrochloride of the methyl base by dissolving the above 1 : 1 salt in water and then saturating the solution with hydrogen chloride. The solution was then allowed to evaporate spontaneously in a desiccator over sulphuric acid, whereupon small, stout, transparent prisms or rhombohedrons separated. The analysis agreed with the calculated for the formula $C_5H_7ON_3 \cdot HCl \cdot 2H_2O$.

	Calculated.	Found.
H ₂ O	18.2	18.0
Cl	21.98	22.0

On keeping these crystals in a closed tube they became opaque.

5-Methylcytosine Basic Hydrochloride.—Experiments were made to determine whether or not 5-methylcytosine gives a 2 : 1 and a 3 : 1 salt by mixing solutions of the base and the above hydrochloride in the required proportions. It was found that when a strong solution of the base (0.12 gram) was mixed with a warm solution of the hydrochloride (0.153 gram) in a little water a precipitate was formed immediately. This dissolved on boiling, and on cooling, little balls of mi-

nute needles or prisms separated. When dried over calcium chloride the salt was found to have the composition represented by Analysis I. When two molecular proportions of the base to one of the hydrous hydrochloride were used the same basic salt was obtained. For example: 0.15 gram of the hydrochloride was dissolved in 2.5 cc. of water and 2.2 grams of the base were dissolved in 5 cc. of water. On mixing these solutions at ordinary temperature a gelatinous mass separated, so bulky that the test-tube could be inverted without loss of the contents. On warming, the material dissolved and on cooling small prisms separated. Analysis II.:

	Calculated for (C ₅ H ₇ ON ₃) ₂ HCl.H ₂ O.	I.	Found. II.
H ₂ O	5.9	6.2	5.9
Cl	11.6	11.3	

This hydrous basic salt is analogous to the hydrous basic cytosine sulphate frequently obtained by Levene.¹ This salt has the formula (C₄H₅ON₃)₄H₂SO₄.2H₂O.

The corresponding anhydrous basic sulphate has been described by Kossel and Steudel.²

A neutral sulphate of cytosine has also been described by Levene.³

5-Methylcytosine Basic Hydrobromide.—Ten grams of 2-ethyl-mercapto-5-methyl-6-aminopyrimidine were boiled with 15 cc. of strong hydrobromic acid for four hours. The acid was then evaporated, whereupon beautiful, large, stout prisms separated. These crystals were very soluble in water. Upon adding strong ammonia to the warm aqueous solution an immediate precipitate in the form of a fine, crystalline powder was obtained. The yield was 7 grams. This precipitate was difficultly soluble in water. When heated it sintered at about 295° and then decomposed with effervescence at 319°–320°. This material was boiled for some time with strong aqueous ammonia; it nevertheless still contained bromine, and on analysis the following results were obtained: The air-dried salt lost water very slowly below 150°, dried at 175°–185°.

¹ Ztschr. physiol. Chem., 39, 7; 39, 135, 481 (1903).

² *Ibid.*, 38, 53 (1903).

³ *Ibid.*, 37, 495 (1903).

0.4838 gram lost 0.0290 gram water or 5.9 per cent. The calculated for $(C_5H_7ON_3)_2HBr \cdot H_2O$ is 5.1 per cent. The dried residue then gave the following results :

	Calculated for $(C_5H_7ON_3)_2HBr$.	Found.
C	36.25	36.20
H	4.53	4.85
N	25.37	25.68

This basic salt was then treated with silver sulphate as described above in the case of the basic hydrochloride. The free base obtained agreed in every particular with the preparation from the basic hydrochloride. A water determination is given above (II.).

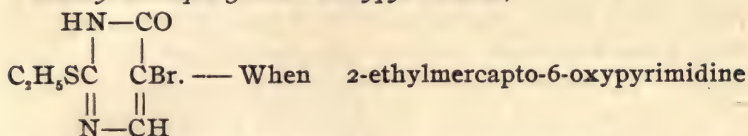
When 0.7 gram of this basic salt was heated at 150° – 160° for three hours with 20 per cent sulphuric acid, 0.20 gram of thymine, melting at 325° – 326° , was obtained. Forty per cent of the material was therefore hydrolyzed.

Acetyl-5-methylcytosine, prepared by dissolving the base in acetic anhydride, forms needles from water. The material did not melt or effervesce below 290° although it showed signs of decomposition at about 255° .

5-Methylcytosine Picrate.—When 0.238 gram of the base in a little water was mixed with 40 cc. of a saturated aqueous solution of picric acid, an immediate precipitate was formed. This dissolved on boiling and adding more water; on cooling, long, slender, bright yellow, needle-like prisms separated. On heating, this material showed signs of change at about 250° – 255° and from then on got darker until at 286° it decomposed with effervescence. A certain mixture of this material with pure cytosine picrate began to change color, on heating, at 255° and melted with effervescence at 273° . It is noteworthy that this picrate has the same solubility in water as cytosine picrate.¹ One hundred parts of water dissolve 0.07 part of the salt.

The *chloroplatinate* is quite soluble in water. The aqueous solution, on standing in a desiccator, deposits small orange-colored rosettes.

¹ Wheeler and Johnson : *Loc. cit.*

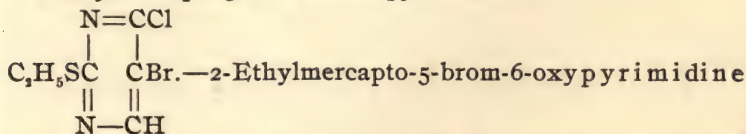
2-Ethylmercapto-5-brom-6-oxypyrimidine,

(5.55 grams) was dissolved in three parts of glacial acetic acid and one molecular proportion of bromine was added (6 grams), a mass of needles separated; these were washed with water and dried; the weight was 7.45 grams or 89 per cent of the calculated. In another experiment 16 grams of the mercapto compound gave 22.1 grams of the brom-derivative or 91.7 per cent of the theoretical amount. This material was difficultly soluble in water, but more readily soluble in alcohol, from which solution beautiful, colorless, needle-like prisms were obtained. These, on heating, showed signs of change at about 184° and melted completely without effervescence at 189° . A nitrogen determination gave:

	Calculated for $\text{C}_6\text{H}_7\text{ON}_2\text{SBr}$.	Found.
N	11.9	12.1

An excess of bromine does not effect further substitution in the cold. When the substance is boiled with hydrochloric acid, 5-bromuracil is obtained.¹ Dr. Merriam found that when this latter substance was heated with aqueous ammonia to 180° , 5-aminouracil resulted, the compound being identified by means of its picrate.²

The action of alcoholic ammonia on the brommercapto compound at temperatures between 140° and 200° did not lead to a smooth result.

2-Ethylmercapto-5-brom-6-chlorpyrimidine,

(21 grams) and phosphorus pentachloride (18.6 grams) were mixed and warmed on the steam-bath. After standing over

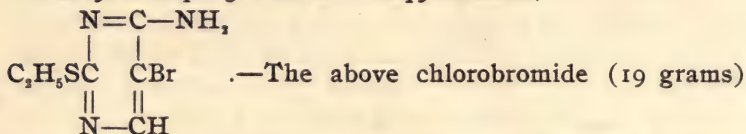
¹ Wheeler and Merriam: *Loc. cit.*

² Behrend and Grünwald: *Ann. Chem. (Liebig)*, 309, 258 (1899).

night the phosphorus oxychloride was removed by distilling under diminished pressure and the remaining oil poured off from a small amount of resin; this was washed with a little ether. The weight of crude oil then obtained, on evaporating the ether, was 20.5 grams or 92 per cent of the calculated. On standing, this oil solidified in the form of soft, talc-like, colorless plates which, when pressed on paper, melted at about 27°. A nitrogen determination then gave:

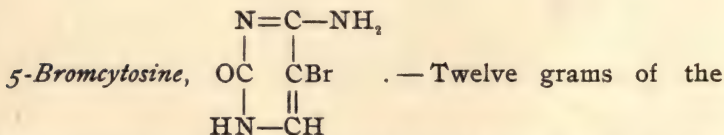
	Calculated for $C_6H_5N_2SClBr$.	Found.
N	11.04	11.06

2-Ethylmercapto-5-brom-6-aminopyrimidine,



was heated with alcoholic ammonia (40 cc. cold saturated solution) to 160° for four hours. On cooling, a crystalline mass separated with little or no color. Water was added to the contents of the tube; the material that separated, on drying, weighed 15.7 grams or 89.7 per cent of the calculated. The substance was readily soluble in hot alcohol and difficultly in cold, and very difficultly soluble in hot water. On crystallizing from alcohol it formed beautiful, colorless prisms which melted sharply at 123° to 124°. The material contained sulphur and bromine, and a nitrogen determination gave the following result:

	Calculated for $C_6H_5N_2SBr$.	Found.
N	17.9	17.8

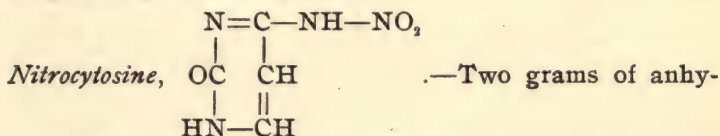


above mercapto compound were boiled with 50 cc. of concentrated hydrochloric acid for four or five hours. The acid was then evaporated and the residue crystallized from water,

whereupon minute prisms of the hydrochloric acid salt were obtained. To the hot solution of this material strong ammonia was added in excess, and then, on cooling, bunches of needle-like prisms of the free base separated. The yield was 7.5 grams, or 77.3 per cent of the calculated, more being obtained from the mother-liquor. When the pure base, crystallized from water, was heated it gave no definite melting-point but decomposed rapidly above 235°. A nitrogen determination gave :

	Calculated for $C_4H_4ON_3Br$.	Found.
N	22.10	22.11

When this material was heated at 155° to 190° with concentrated aqueous ammonia for four hours, the products were a black resin and a brick-red amorphous powder, the material having undergone decomposition.



drous cytosine (synthetic), 4. cc. of concentrated nitric acid, and 4 cc. of concentrated sulphuric acid were mixed and warmed for a few minutes at 85°. The mixture was then poured upon crushed ice and neutralized (slight excess of ammonia added). The crystalline material that separated weighed 1.8 grams, or 64 per cent of the calculated. In another experiment 2 grams of cytosine and 6 cc. of each acid gave 1.7 grams of the crude nitro compound. This nitro compound is very difficultly soluble in water, from which it separates in the form of colorless, minute needles. These are readily soluble in strong ammonia. When heated, the material begins to turn brown at about 280°, decomposes rapidly above 300°, but does not melt or effervesce at 350°. A nitrogen determination gave the following result :

	Calculated for $C_4H_4O_3N_4$.	Found.
N	35.89	35.80

When an attempt was made to reduce this material with

tin and hydrochloric acid the only crystalline material obtained was ammonium chloride. According to Behrend and Grünwald¹ 5-nitrouracil gives 80 per cent of the calculated of aminouracil, when reduced in ammoniacal solution by means of aluminium amalgam. An attempt to reduce our nitrocytosine in a similar manner gave nothing but amorphous yellow and blue-black decomposition-products. For this reason the above nitramide structure is assigned to the compound.

NEW HAVEN, CONN., Feb. 1, 1904.

¹ *Loc. cit.*

[Reprinted from the American Chemical Journal, Vol. XXXII, No. 2.
August, 1904.]

Contributions from the Sheffield Laboratory of Yale University.

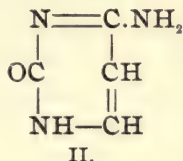
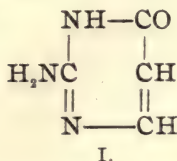
CXV.—RESEARCHES ON PYRIMIDINES. SYNTHESIS OF 2-AMINO-5-METHYL-6-OXYPYRIMIDINE.

[SIXTH PAPER.]

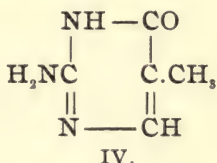
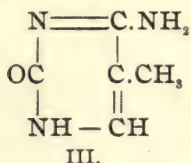
BY TREAT B. JOHNSON AND SAMUEL H. CLAPP.

In a previous paper from this laboratory, Wheeler and

Johnson¹ described the two monoaminooxypyrimidines which can give uracil on hydrolysis, *viz.*, 2-aminooxypyrimidine (Formula I.), and 2-oxy-6-aminopyrimidine or cytosine (Formula II.):



In a similar manner the two monoaminomethylpyrimidines which could give thymine on hydrolysis are, *viz.*, 2-oxy-6-amino-5-methylpyrimidine (Formula III.) and 2-amino-6-oxy-5-methylpyrimidine (Formula IV.):



Wheeler and Johnson² in a recent paper have described 2-oxy-6-amino-5-methylpyrimidine (Formula III.) and have shown that it is more or less readily converted into thymine on hydrolysis.

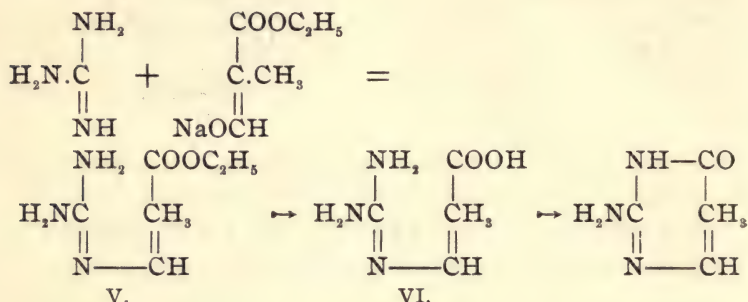
We will describe in this paper the second monoaminomethylpyrimidine (Formula IV.), which theoretically could give thymine on hydrolysis, *viz.*, 2-amino-5-methyl-6-oxypyrimidine. We have synthesized this aminopyrimidine by condensing guanidine with the sodium salt of formylethylpropionate. We have not only been able to obtain the pyrimidine base which we desired, but have also succeeded in isolating intermediate products in the reaction. These have given us a more thorough insight into the mechanism of these pyrimidine condensations.

We find, namely, that in this condensation there are three steps in the reaction—first a condensation of guanidine with

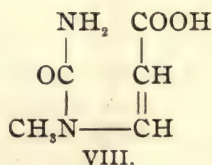
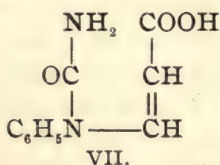
¹ This JOURNAL, 29, 492 (1903).

² *Ibid.*, 31, 592 (1904).

the formyl group of the sodium formylethylpropionate giving an acrylic ester (Formula V.), then a saponification of the acrylic ester to the free acid (Formula VI.), and finally a condensation to the pyrimidine with loss of a molecule of water :



Under the conditions by which we worked we did not observe the formation of the intermediate guanidineacrylic ester, but have evidence of its existence because of the fact that we have been able to isolate the intermediate guanidine-methylacrylic acid. Müller¹ has described two substituted acrylic acids that are analogous to our intermediate acid. He found that phenylurea and methylurea readily condensed with oxalethylacetate, giving a phenyluracilcarboxylic ester and methyluracilcarboxylic ester. By dissolving these two esters in alkali and treating with strong hydrochloric acid they were decomposed into uramidoacrylic acids (Formulas VII. and VIII.) :



Behrend,² in his synthesis of methyluracil from acetoacetic ester and urea, was able to isolate an intermediate uramido-crotonic ester, but was unable to isolate the free acid from its

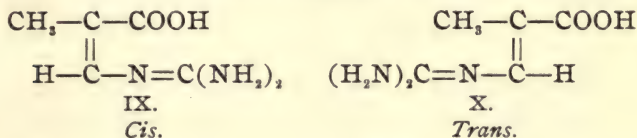
¹ J. prakt. Chem., 56, 475.

² Ann. Chem. (Liebig), 229, 8.

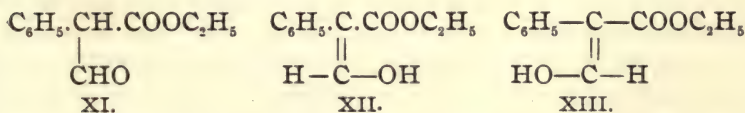
sodium or potassium salt on account of the ease with which it condensed to the pyrimidine.

We, furthermore, have made the interesting observation that our intermediate α -methyl- β -guanidineacrylic acid is capable of existing in two isomeric modifications. One acid melts at 331° to 332° C. with violent effervescence ; the other at 318° to 320° C. to a clear oil. Both acids can be converted by treatment with alkali into the 2-amido-5-methyl-6-oxy-pyrimidine.

It appears to us that the explanation for this interesting case of isomerism is that we are dealing with an ethylene linking, and have another case of *cis* and *trans* isomerism :



Wislicenus¹ was able to isolate three isomeric modifications of formylphenylethylacetate. He represented their structure as follows :



He furthermore showed that the *enol* form was capable of forming isomeric salts, which gave isomeric acyl modifications when treated with acyl chlorides.

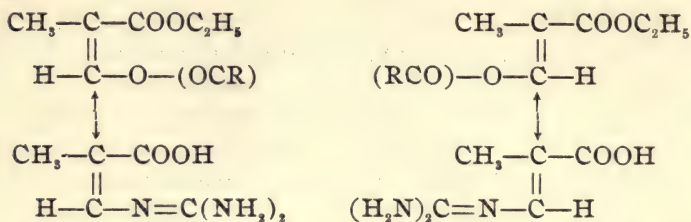
In a later paper Wislicenus and Bindemann² showed that analogous acyl modifications could be obtained from the sodium salt of formylethylacetate. Finally, Wislicenus³ extended his investigations to the sodium salt of formylethyl-propionate, which we used in our condensation, and observed that this also gave stereochemical isomers when treated with acyl chlorides. The close analogy between Wislicenus' iso-

¹ Ann. Chem. (Liebig), 312, 33.

² Ibid., 316, 18.

³ Ibid., 316, 333.

mers and our modifications is shown by the following formulas :



It seems probable to the writer that Pechmann's¹ isomeric derivatives which he obtained by treating the sodium salt of formylethylacetate with aniline and paratoluidine are to be explained in a similar manner :



Erlenmeyer² has shown that ethyl formate can be condensed with hippuric ethyl ester by means of sodium ethylate to the sodium salt of oxymethylenhippuric ester. We have prepared this salt and find that it condenses very smoothly with pseudoethylthiourea, giving 2-ethylmercapto-5-benzoylamino-6-oxypyrimidine.

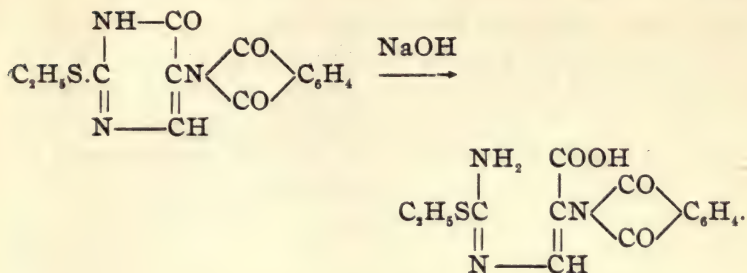
We, furthermore, have condensed ethyl formate with phthalimidoethylacetate to the sodium salt of formylphthalimidoethylacetate. We find that this salt condenses with pseudoethylthiourea with the formation of 2-ethylmercapto-5-phthalimido-6-oxypyrimidine, and an intermediate acrylic acid.

The two above pyrimidines show a most striking behavior towards alkali. 2-Ethylmercapto-5-benzoylamino-6-oxypyrimidine dissolves in alkali and is precipitated unaltered by acids, while, on the other hand, the analogous 2-ethylmercapto-5-phthalimido-6-oxypyrimidine is converted under the same conditions into the corresponding pseudoureaphthalimidoacrylic acid.³

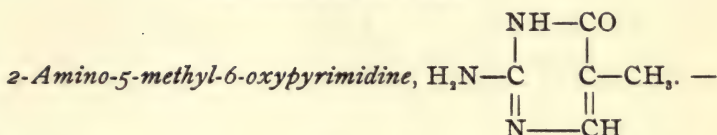
¹ Ber. d. chem. Ges., 25, 1052.

² Ibid., 36, 3769.

³ Since the above was written we have found that 2-ethylmercapto-5-benzoylamino-6-oxypyrimidine is converted by alkali into the sodium salt of the corresponding pseudoureabenzoylaminoacrylic acid. We have not succeeded in isolating the free acid.



EXPERIMENTAL PART.



Seventy-two grams of guanidine carbonate were dissolved in the least possible quantity of cold water and mixed with 54 grams of barium hydroxide dissolved in 400 cc. of water. To this solution, filtered clear from the precipitated barium carbonate, 283 grams of crude sodium formylethylpropionate were added. After standing at ordinary temperature for about eight hours the clear solution was divided into two equal parts. One part was heated on the steam-bath for about half an hour and then neutralized with dilute sulphuric acid. A brown precipitate separated immediately and was filtered off and saved (see *trans* acid). The clear solution that remained was evaporated to dryness, then redissolved in a little warm water, and filtered from a small amount of insoluble material that was present. The pyrimidine base was then precipitated with phosphotungstic acid, the tungstic acid precipitate decomposed with barium hydroxide, and the excess of barium hydroxide removed in the usual way with carbon dioxide. On concentrating the solution that remained, and cooling, the base separated in the form of stout prisms and melted with effervescence at 320° to 321°.

The second part of the original solution was allowed to stand at ordinary temperature for two weeks. It was then neutralized with dilute sulphuric acid as before. An insoluble

ble brown precipitate was obtained as in the first part. After filtering off this insoluble precipitate we precipitated the pyrimidine base with mercuric chloride instead of phosphotungstic acid. The mercury was removed from the precipitate with hydrogen sulphide and then the base allowed to crystallize from the concentrated solution.

The yield of pure base by the two different methods of treatment was about equal (4 grams), showing that long standing does not increase to any extent the yield. The same observation was made by Wheeler and Johnson¹ in their preparation of isocytosine or 2-amino-6-oxypyrimidine.

2-Amido-5-methyl-6-oxypyrimidine crystallized from hot water in two distinct crystalline forms, stout prisms, and long, slender, needle-like prisms. It melts at 320° to 321° with violent effervescence. It does not contain water of crystallization. One hundred parts of water dissolve 0.43 part base at 25° C. A nitrogen determination gave:

	Calculated for $C_5H_7ON_3$.	I.	Found.	II.
N	33.60	33.68		33.91

The base was not hydrolyzed to thymine after heating in a sealed tube with 25 per cent sulphuric acid for five hours.

In a second condensation we modified our experiment in the following manner: After adding the sodium formyl-ethylpropionate to the guanidine solution, we added a molecular proportion of sodium hydroxide (29 grams). The alkaline solution was then allowed to stand at a temperature of 40° to 50° for about ten hours, and then heated on the steam-bath for three hours. The solution was then divided into two equal parts and one part neutralized with acetic acid, the other with dilute sulphuric acid. An immediate precipitate of the *trans* acid resulted in both cases. The weight of insoluble acid obtained here was 12.2 grams.

The two filtrates were combined and precipitated with an excess of mercuric chloride. The mercury was removed in the usual way with hydrogen sulphide and the filtrate concentrated. On cooling the concentrated solution we obtained

¹ *Loc. cit.*

a mass of needle-shaped prisms mixed with stout prisms. Some of these needle-formed prisms melted at 319° to 320° to a clear oil, followed by a slow effervescence. That this body was not the same product as we obtained in our first condensation was shown by the fact that when it was mixed with the free pyrimidine the melting-point was lowered to 308° – 310° (see *cis* acid). The yield of this crystalline product was 18.2 grams.

Behavior with Alkali.—The base dissolves very readily in the cold in both dilute (2 per cent) and strong (9 per cent) solutions of sodium hydroxide, and is precipitated unaltered when the alkaline solution is neutralized with carbon dioxide or dilute sulphuric acid. It separates in the form of needle-formed prisms and melts at 320° to 321° with violent effervescence. In appearance this crystalline form of the base resembles very much that of the *cis* acid. That the ring is not opened by the treatment with alkali is shown by the fact that when this body was mixed with the *cis* acid the melting-point was lowered to 307° . Furthermore, a nitrogen determination gave:

	Calculated for $C_6H_7ON_3$.	Found.
N	33.60	33.90

The Hydrochloride.—Some of the base was dissolved in concentrated hydrochloric acid and the solution concentrated in a vacuum. The hydrochloride separated in stout prisms. A chlorine determination agreed with the calculated for monohydrochloride:

	Calculated for $C_6H_7ON_3.HCl$.	Found.
Cl	21.98	21.73

The Picrate.—The picrate separated immediately from water in yellow, microscopic crystals. They were practically insoluble in boiling alcohol and water. After prolonged boiling with water the insoluble picrate was filtered off and analyzed for nitrogen:

	Calculated for $C_6H_7ON_3.C_6H_3O_7N_3$.	Found.
N	23.73	23.92

The Sulphate.—The sulphate crystallized from water in the form of flattened prisms or plates. A sulphur determination agreed with the calculated for an acid salt. It is interesting to note that Jaeger¹ obtained analogous acid sulphates from the isomeric 2-amido-4-methyl-6-oxypyrimidine, and from 2-amido-4,5-dimethyl-6-oxypyrimidine :

S	Calculated for $C_5H_7ON_3.H_2SO_4$.	Found.
	14.34	14.62

Platinum Chloride Double Salts.—Two characteristic platinum chloride double salts were obtained. The first was prepared by adding hydrogen platonic chloride to a cold, dilute hydrochloric acid solution of the base. It analyzed for a salt with 4 molecules of water of crystallization :

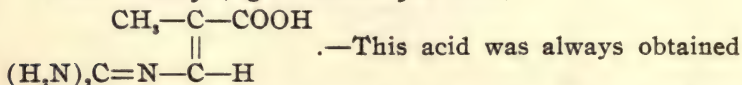
Pt	Calculated for $(C_5H_7ON_3.HCl)_2PtCl_4.4H_2O$.	I.	Found.	II.
	26.56	26.51		26.61

When hydrogen platonic chloride was added to a hot hydrochloric acid solution of the base and then the solution allowed to cool slowly, the platinum salt separated in thick tables and melted at 254° to 255° . A water determination and an analysis for platinum agreed with the calculated for a double platinum salt containing two molecules of water of crystallization :

0.1995 gram salt lost 0.0106 gram H_2O at 120° to 130° C.

Pt H_2O	Calculated for $(C_5H_7ON_3.HCl)_2PtCl_4.2H_2O$.	Found.
	27.99 5.17	27.76 5.30

Trans- α -Methyl- β -guanidineacrylic Acid,



in the condensation described above, when we neutralized the alkaline solution, preliminary to precipitating the pyrimidine base with mercuric chloride. It separated as an amorphous brown precipitate. One of the most characteristic physical properties that distinguished this acid from its *cis* modification and the pyrimidine was its insolubility in water. One hun-

¹ Ann. Chem. (Liebig), 262, 371.

dred parts of water dissolve 0.08 part acid at 25° C. It crystallized from boiling water in poorly developed prisms, and melted according to the rate of heating from 329° to 332° with violent effervescence. It possesses both acid and basic properties. A nitrogen determination gave :

	Calculated for $C_5H_9O_2N_3$.	Found.
N	29.37	29.32

In our second condensation the *trans* acid came down less pure and was mixed with a considerable amount of stout prisms. These were separated by boiling with water. After filtering and cooling, the prisms separated again and melted at 320° to 321° with effervescence. That this was the pyrimidine base was shown by the fact that when mixed with the pure pyrimidine the melting-point was not lowered. The *trans* acid was not changed to the *cis* modification or the pyrimidine after boiling in water for six hours. A nitrogen determination in the above pyrimidine, melting at 320° to 321°, gave :

	Calculated for $C_5H_7ON_3$.	Found.
N	33.60	33.68

Behavior with 9 Per Cent Sodium Hydroxide.—When the *trans* acid was dissolved either in the cold or warm sodium hydroxide solution, and the solution neutralized with carbon dioxide it separated in the form of stout prisms and melted at 320° to 321° with violent effervescence. That this was the pyrimidine base was confirmed by a nitrogen determination :

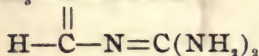
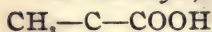
	Calculated for		Found.
	$C_5H_7ON_3$.	$C_5H_9O_2N_3$.	
N	33.60	29.37	33.52

The formation of the pyrimidine from the *trans* acid was furthermore confirmed by the formation and analysis of its platinum chloride salt. It separated in the form of stout prisms and melted at 254° to 255°. When mixed with the double salt previously described as melting at 254° to 255° the melting-point was not lowered. A platinum determination gave :

	Calculated for (C ₅ H ₇ ON ₃ .HCl) ₂ PtCl ₄ .2H ₂ O.	Found.
Pt	27.99	27.93

Behavior with 2 Per Cent Sodium Hydroxide.—Some of the *trans* acid melting at 331° was dissolved in the cold, dilute sodium hydroxide solution. On neutralizing with dilute sulphuric acid it separated again as a brown, poorly crystallized precipitate. It was extremely insoluble in water and melted at 330° to 332° with violent effervescence. The *trans* acid was precipitated again unaltered after this treatment with dilute alkali. When mixed with the pure analyzed acid the melting-point was not lowered. This experiment is of interest because it enabled us to determine the *cis* and *trans* forms of our acid. The isomeric modification could not be precipitated unaltered from an alkaline solution.

Cis-α-Methyl-β-guanidineacrylic Acid,



—This acid was obtained in our sec-

ond condensation when we precipitated with mercuric chloride to obtain the pyrimidine base. After removing the mercury from the precipitate with hydrogen sulphide and concentrating the solution it separated with the pyrimidine base in slender, needle-like prisms. It was obtained pure by recrystallizing from hot water. It was approximately about twice as soluble in water as the pyrimidine. One hundred parts of water dissolve 0.84 part acid at 25°. The most noticeable physical property which this acid possesses is its behavior on melting. It melts at 319° to 320° to a clear oil, followed by a slight effervescence and slow decomposition. A nitrogen determination gave :

	Calculated for C ₆ H ₉ O ₂ N ₃ .	I.	Found.	II.
N	29.37	29.05		29.6

In order to be certain that we were dealing here with a second modification of the guanidineacrylic acid, and not with a modification of our pyrimidine containing water of crystallization, some of the acid was heated for one hour at 115° to 120°, and again at 140° for one hour. The body lost no weight by

this treatment, thus confirming our assumption that we had in hand an isomeric acid.

Behavior with 9 Per Cent Sodium Hydroxide.—The *cis* acid dissolved immediately in the sodium hydroxide solution. When the alkaline solution was neutralized with carbon dioxide or with dilute hydrochloric acid an asbestos-like precipitate of needle-like prisms were obtained. They melted at 319° to 321° with effervescence. When mixed with the pyrimidine (m. p. 320°) the melting-point was not lowered. When mixed with the *cis* acid (m. p. 319° to 320°) the melting-point was lowered to from 302° to 303° . That the *cis* acid had been converted into the pyrimidine was confirmed by a nitrogen determination:

	Calculated for $C_6H_7ON_3$.	Found.
N	33.60	33.23

Behavior with 2 Per Cent Sodium Hydroxide.—The *cis* acid that was used in this experiment melted sharply at 320° to a clear oil and analyzed for 29.05 per cent of nitrogen, calculated 29.37 per cent. It dissolved immediately in the cold, dilute sodium hydroxide solution. When the alkaline solution was neutralized with carbon dioxide or sulphuric acid the base was precipitated in needle-like prisms melting at 320° with effervescence. A nitrogen determination agreed with the calculated for the pyrimidine:

	Calculated for $C_6H_7ON_3$.	Found.
N	33.60	33.43

Acetic acid also precipitated from an alkaline solution of the *cis* acid, the pyrimidine melting at 320° .

Condensation of Ethyl Formate with Phthalimidoethylacetate.—This condensation was effected by suspending the phthalimidoethylacetate in benzene or ether with the calculated amount of sodium and adding slowly the ethyl formate. The condensation was not smooth, and after standing for several hours, with occasional shaking, much phthalimidoethylacetate remained unaltered. From 50 grams of phthalimidoethylacetate about 50 grams of crude sodium salt were obtained.

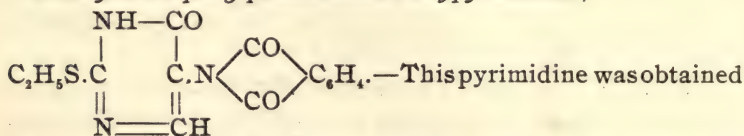
This sodium salt is exceedingly unstable in aqueous solution. Some of the salt was dissolved in water and then filtered. When this clear salt solution was allowed to stand for several hours at ordinary temperature it gradually deposited a crystalline solid. This crystallized from alcohol in needle-like prisms and melted at 111° . It proved to be unaltered phthalimidoethylacetate. When the filtered solution was acidified with hydrochloric acid no further precipitation took place.

On the other hand, when a solution of the sodium salt was immediately acidified with hydrochloric acid a semisolid precipitate was obtained. It was insoluble in hot water. It dissolved in cold alcohol with the exception of a small amount of white, crystalline material. This insoluble product crystallized from hot alcohol in needles and melted at 193° to 194° . It was soluble in alkali to a yellow solution. This body was identified as 4-oxyisoquinoline-3-carboxylic ethyl ester, which was obtained by Gabriel and Colman¹ by heating phthalimidoethylacetate with sodium ethylate and alcohol at 100° . A nitrogen determination gave:

	Calculated for $C_{12}H_{11}O_4N$.	Found.
N	6.00	6.21

When the above alcoholic extract was evaporated to dryness a thick syrup was obtained which immediately solidified on cooling. It crystallized from alcohol in prisms and melted at 111° to 112° . It was identified as phthalimidoethylacetate.

2-Ethylmercapto-5-phthalimido-6-oxypyrimidine,



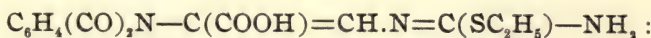
by condensing pseudoethylthiourea in aqueous solution with the sodium salt of formylphthalimidoethylacetate. Six and two-tenths grams of the crude salt were treated with 160 cc. of water and filtered from the unaltered phthalimidoethylacetate. To the clear solution was then added an aqueous solution of

¹ Ber. d. chem. Ges., 33, 983.

the pseudourea, that was prepared by mixing a solution of 36 grams of the hydrobromide with 11 grams of potassium hydroxide. The resulting mixture was then allowed to stand at ordinary temperature for one hour, and then heated on the steam-bath. Mercaptan was evolved in large amount, and on prolonged heating the solution assumed a dark-green color. A crystalline precipitate finally began to separate from the hot solution when the mixture was removed from the bath and allowed to cool. This crystalline body proved to be phthalimidoethylacetate. On acidifying the solution with sulphuric acid a thick, gummy precipitate was obtained, which was purified by boiling with water and animal charcoal. It crystallized from alcohol in rhombic plates and melted at 230° to 231° to a yellow oil. It gave a strong test for sulphur. A nitrogen determination gave :

	Calculated for $C_{14}H_{11}O_5N_3S$.	Found.
N	13.95	14.3

When the above pyrimidine was dissolved in alkali and then acidified with dilute hydrochloric or sulphuric acid a white, crystalline precipitate was immediately obtained. It crystallized from 50 per cent alcohol and melted with violent effervescence at 130° to 131° , then solidified again in the hot bath, and did not melt again until 229° to a clear, yellow oil. It gave a strong test for sulphur. A nitrogen determination agreed with the calculated for α -phthalimido- β -pseudoethylthioureaacrylic acid,

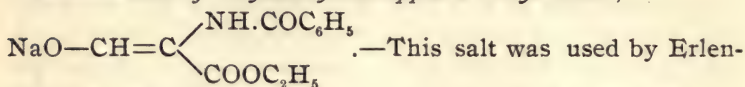


	Calculated for $C_{14}H_{13}O_4N_3S$.	Found.
N	13.16	13.26

This same acid was obtained in the above condensation when the acid filtrates were allowed to stand. It separated in small prisms and was purified by crystallizing from alcohol. When the acid was heated above its melting-point in an oil-bath it immediately decomposed with loss of a molecule of water, giving the pyrimidine derivative melting at 231° .

When mixed with the pyrimidine the melting-point was not lowered.

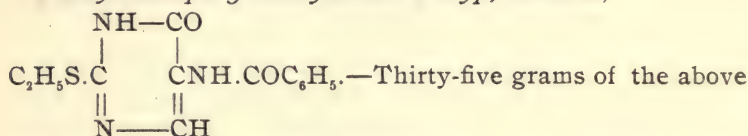
Sodium Salt of Oxymethylenehippuric Ethyl Ester,



meyer¹ in his synthesis of serine and cystine. He gives no directions for preparing the salt, but states that he obtained it by condensing ethyl formate with hippuric ethyl ester in presence of sodium ethylate.

We have prepared the salt by condensing hippuric ethyl ester with ethyl formate in benzene in the presence of metallic sodium. The condensation is very slow. From 25 grams of hippuric ester we obtained 35 grams of the crude salt.

2-Ethylmercapto-5-benzoylamino-6-oxy-pyrimidine,



sodium salt were dissolved in cold water and combined with an aqueous solution of pseudoethylthiourea. Only 0.5 molecular proportion of pseudourea was used in this reaction, or 13 grams of the hydrobromide, which were neutralized with 4 grams of potassium hydroxide. The mixture was allowed to stand at ordinary temperature for forty-eight hours. No odor of mercaptan was noticeable. When the mixture was examined a large amount of crystalline material had separated from the aqueous solution. This crystallized from alcohol in needles and melted at 238° to 239° to a yellow oil. It gave a strong test for sulphur and did not decompose when heated to 260°. A nitrogen determination gave:

	Calculated for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}_8\text{S}$.	Found.
N	15.27	15.50

The pyrimidine was soluble in alkali and was precipitated unaltered by hydrochloric acid.

¹ Ber. d. chem. Ges., 36, 3769; 35, 2720.

When the alcoholic filtrates from the above purification were combined and evaporated to dryness an oil was obtained which finally solidified. It was identified as unaltered hippuric ester.

More of the above pyrimidine was obtained by acidifying the original solution after filtering off the crystalline material that had separated. It was precipitated as a semisolid, which quickly solidified on cooling. It crystallized from alcohol in needles and melted at 238° to 239° .

NEW HAVEN, CONN., Feb. 24, 1904.

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Contributions from the Sheffield Laboratory of Yale University.

CXIX.—RESEARCHES ON PYRIMIDINES: 2-OXY-
4,6-DIAMINOPYRIMIDINE.¹

[SEVENTH PAPER.]

BY HENRY L. WHEELER AND GEORGE S. JAMIESON.

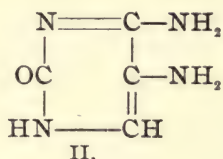
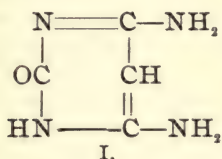
In this paper we describe a number of pyrimidines derived from 2-thiobarbituric acid. Our chief object in investigating

¹ Part of a thesis presented by Mr. G. S. Jamieson for the degree of Doctor of Philosophy, Yale University, 1904.

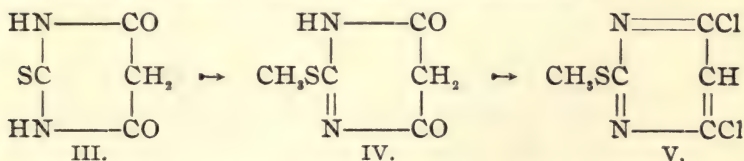
these compounds was to prepare 2-oxy-4,6-diaminopyrimidine.

Kutscher¹ believes he obtained an oxydiaminopyrimidine from yeast nucleic acid, the acid having been decomposed by sulphuric acid at a high temperature and under pressure. He considers the substance as differing from cytosine inasmuch as a hydrogen atom is replaced by an amino group.

It may be added that since the pyrimidine derivatives hitherto obtained from nucleic acids have an oxygen atom in the 2-position, for example, uracil, thymine, and cytosine, it is probable that a diamino derivative would be similarly constituted. This being the case, there are only two oxydiaminopyrimidines that fulfil these conditions, namely, 2-oxy-4,6-diaminopyrimidine (I.) and 2-oxy-5,6-diaminopyrimidine (II.) :



Our first attempts to prepare the oxydiaminopyrimidine represented by Formula I. were as follows: 2-Thiobarbituric acid (III.) was prepared by the method of Michael.² It was found that this substance could be converted into 2-methylmercapto-4,6-dioxypyrimidine (IV.) by means of sodium ethylate and methyl iodide in alcoholic solution :



When the mercapto derivative (IV.) was heated on the steam-bath with 2 molecular proportions of phosphorus pentachloride, it was converted into 2-methylmercapto-4,6-dichloropyrimidine (V.). The reaction was not smooth and a con-

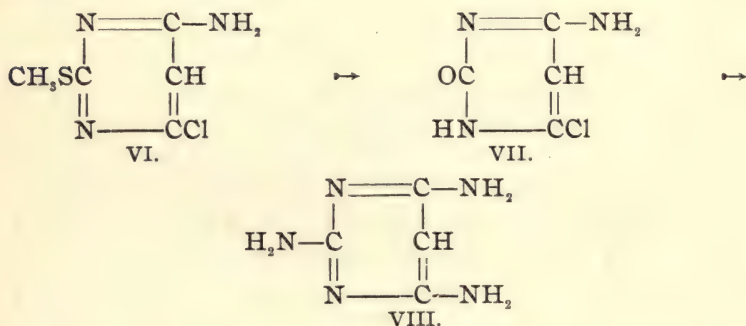
¹ Ztschr. physiol. Chem., **38**, 176 (1903).

² J. prakt. Chem., **35**, 456 (1887) ; **49**, 38 (1894).

siderable amount of decomposition-products was always obtained. It was later observed that the dichloride could be obtained more smoothly by using phosphorus oxychloride instead of the pentachloride.

When the dichloride was heated with alcoholic ammonia it was found that only one chlorine atom was easily removed and 2-mercapto-5-chlorcytosine (VI.) was formed. This took place at temperatures ranging from 125° to about 190°. Even below the latter temperature mercaptan was evolved, and above 190° 2,4,6-triaminopyrimidine (VIII.), which has been described by Gabriel,¹ was obtained. There seemed to be little tendency for the two chlorine atoms to react without also displacing the mercapto group.

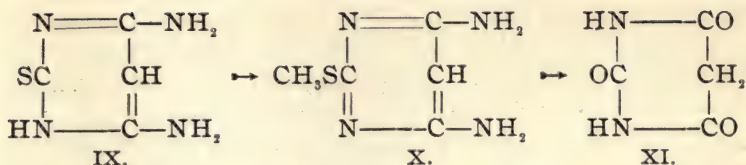
The 2-mercapto-4-chlorcytosine was then converted into 4-chlorcytosine (VII.) by boiling with hydrochloric acid. When this was heated with alcoholic ammonia a reaction took place, but the chief product was not the desired 2-oxy-4,6-aminopyrimidine :



It was finally found that 2-oxy-4,6-diaminopyrimidine could easily be prepared from 2-thio-4,6-diaminopyrimidine (IX.) which Traube² has recently obtained by condensing malonic nitrile with thiourea. This substance united smoothly with methyl iodide and the resulting mercapto derivative (X.) formed on treating the addition-product with ammonia, on carefully boiling with hydrochloric acid, gave the 2-oxy-4,6-diaminopyrimidine (I.) :

¹ Ber. d. chem. Ges., 34, 3364.

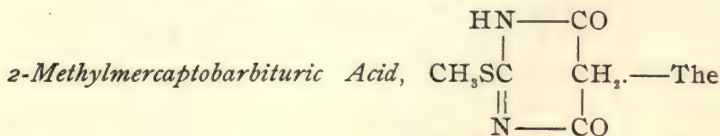
² Ann. Chem. (Liebig), 331, 80 (1904).



It was then found that if the warming with hydrochloric acid was continued for more than a short time on the steam-bath the 2-oxy-4,6-diaminopyrimidine was completely converted into barbituric acid (XI.). It is therefore obvious, from the readiness with which this compound is decomposed by hydrochloric acid, that it is not identical with Kutscher's new base. If the latter is an oxydiaminopyrimidine it probably is 2-oxy-5,6-diaminopyrimidine.

EXPERIMENTAL PART.

2-Thiobarbituric acid was prepared according to Michael's¹ directions, by the condensation of sodium ethyl malonate with thiourea in absolute alcoholic solution. Twenty-five grams of ethyl malonate gave 20 grams of crude sodium thiobarbiturate. From this a yield of 12 grams of acid was obtained. It was found that if instead of the calculated quantity of sodium ethylate two molecular proportions were used a larger yield of the acid resulted. For example, in two experiments, using 25 grams of ethyl malonate, 27 grams of sodium thiobarbiturate were obtained; in three other cases, using the same proportions, 28 grams of salt separated, the yield of thiobarbituric acid in each case being 16.5 grams.



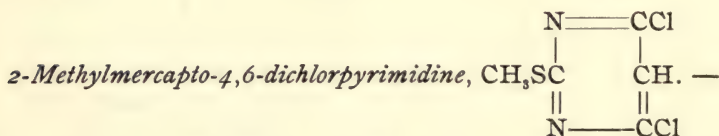
best yield of this substance was obtained when 12 grams of thiobarbituric acid were added to a cold, absolute alcoholic solution of 1.9 grams of sodium, then 15 grams of methyl iodide were added and the solution was not allowed to warm. The reaction was complete in two days. The alcohol and

¹ J. prakt. Chem., **35**, 456 (1887); **49**, 38 (1894).

excess of methyl iodide were then evaporated and the residue was treated with water and acidified with acetic acid. The precipitate was filtered, washed with water, absolute alcohol, and ether. A yield of 8.6 grams of sodium-free material was obtained. In another experiment, 40 grams of acid gave 2.5 grams of the mercapto derivative, the usual yield being between 53 and 66 per cent of the calculated. Attempts to methylate thiobarbituric acid by other methods, such as by direct addition of methyl iodide, or by the action in alcoholic ammonia, or in aqueous solution and in the presence of alkali, either failed entirely or did not give as satisfactory results as the above method.

The 2-methylmercaptobarbituric acid crystallized from water in needles. It is sparingly soluble in hot water and less soluble in alcohol. It did not melt at 300° , but gradually turned a light-brown. A nitrogen determination gave :

	Calculated for $C_5H_6O_2N_2S$.	Found.
N	17.72	17.87

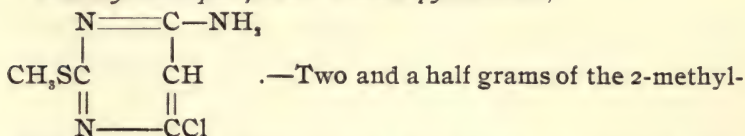


Four grams of the above 2-methylmercaptobarbituric acid were heated with 9 grams of phosphorus pentachloride on the steam-bath. When the evolution of hydrogen chloride ceased the dark-red solution was cooled and treated with crushed ice. The dichloride was then shaken out with ether, the ethereal solution dried over calcium chloride, evaporated, and the residue distilled at 28 mm. pressure, whereupon 2.5 grams of colorless oil were obtained, boiling at 154° , this being a yield of 50.2 per cent of the calculated. In two other experiments with phosphorus pentachloride, using in each case 8 grams of the methylmercaptobarbituric acid, 3 grams and 3.7 grams of dichloride were obtained. Both specimens boiled at 135° to 136° at 14 mm. pressure. The oil thus obtained solidified in the form of table-like prisms, which melted at 41° to 42° . When phosphorus oxychloride was used instead

of the pentachloride, the remaining treatment being the same, the dichloride was directly obtained in the crystalline condition, it being unnecessary to distil under reduced pressure. The material from the ethereal solution was purified by recrystallizing from a little alcohol. It then formed stout, pointed prisms and the melting-point was not altered. It is very soluble in ether, alcohol, and petroleum ether. In two experiments, using 5 grams of the methylmercaptobarbituric acid, 3.3 grams and 3.4 grams of the dichloride were obtained. The yield by the action of either the pentachloride or the oxychloride of phosphorus, especially in large quantities, was found to be very irregular. A nitrogen determination gave:

	Calculated for $C_5H_4N_2SCl_2$.	Found.
N	14.36	14.76

2-Methylmercapto-4-chlor-6-aminopyrimidine,



mercapto-4,6-dichlorpyrimidine were heated in a sealed tube with about 75 cc. of alcoholic ammonia for four hours at 125° to 126° . On cooling, the ammonium chloride which had separated was filtered and the filtrate evaporated. The residue was purified by recrystallizing from water, in which it was difficultly soluble. It crystallized in colorless, needle-like prisms, which melted at 127° to 128° to a colorless liquid. A yield of 1.5 grams of purified material was obtained. Four other experiments gave the following yields:

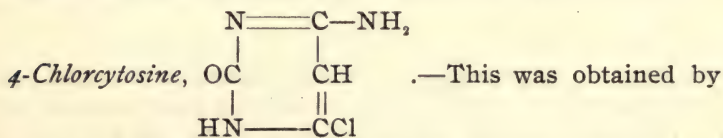
Chloride. Grams.	Monoamine. Grams.
3.7	2.6
3.0	2.2
3.2	2.7
3.3	2.6

A nitrogen determination gave:

	Calculated for $C_5H_6N_2SCl$.	Found.
N	23.93	24.04

Action of Alcoholic Ammonia.—This chloraminopyrimidine (1.1 grams) was heated with about 75 cc. of alcoholic ammonia (alcohol saturated with dry ammonia at 0°) at 145° for three hours and then for two hours at 150°, whereupon the material was recovered completely unaltered. The 1.1 grams of substance were reheated with the same volume of fresh alcoholic ammonia at 170° for two hours, and then at 190° for a half hour; 0.7 gram of unaltered material was obtained.

Two and four-tenths grams of the chloraminopyrimidine were heated with alcoholic ammonia for two hours at 185° to 190°, and four hours at 215° to 220°. On opening the tube the alcohol was found to be saturated with mercaptan. A considerable amount of a light-yellow precipitate had separated from the alcohol. This was filtered, washed with alcohol and then with water. It melted at about 234° to 240° and it gave an alkaline reaction to turmeric paper. It contained neither sulphur nor chlorine and was found to be 2,4,6-triaminopyrimidine, which has been described by Gabriel.¹



boiling 0.5 gram of the above mercapto derivative with concentrated hydrochloric acid. Mercaptan was readily evolved and upon evaporating the solution, 4-chlorcytosine hydrochloride was obtained. This crystallized from hot water in balls of very small, slender, hard prisms or needles. From dilute aqueous solutions of this salt, ammonia precipitates a crop of flat, colorless prisms; from more concentrated solutions the base separates as a jelly resembling thick starch paste, which is difficult to filter. When dried on paper it adheres strongly to the fiber. It is fairly soluble in water and it does not melt at 300°, although it sinters and gradually turns red. A nitrogen determination gave:

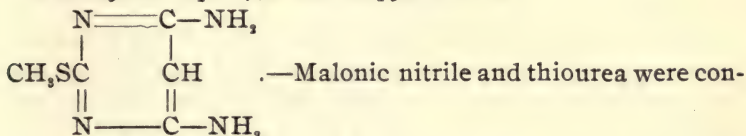
	Calculated for $\text{C}_4\text{H}_4\text{ON}_3\text{Cl}$.	Found.
N	28.86	28.73

¹ Ber. d. chem. Ges., 34, 3364.

The chlorine in this compound is very firmly bound. It was not removed by tin and hydrochloric acid, or by red phosphorus and hydriodic acid.

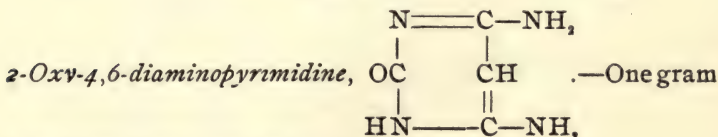
When 1.5 grams of this material were heated with alcoholic ammonia at 183° for two hours 0.95 gram of substance insoluble in alcoholic ammonia was formed. It was difficultly soluble in water; if the solution was cooled rapidly, very small crystals were obtained; if slowly cooled, little balls were formed. This substance did not melt at 307° . It was free from chlorine and a nitrogen determination gave only 24.9 per cent nitrogen. It was not identified, since two attempts to prepare the compound failed on account of the explosion of the sealed tubes and no time was available to repeat the work.

2-Methylmercapto-4,6-diaminopyrimidine,



densed according to Traube's¹ directions in an alcoholic solution with sodium ethylate. Two grams of the 2-thio-4,6-diaminopyrimidine were moistened with alcohol and 2.2 grams of methyl iodide were added. The mixture stood two hours without change. Suddenly, heat was evolved and the solution solidified. The alcohol was evaporated and the residue was dissolved in water. Ammonia then precipitated 2.2 grams of colorless crystalline material. This was quite soluble in hot water, from which, on cooling, it separated in the form of slender prisms. It melted at 185° to 186° with a little effervescence, and a nitrogen determination gave :

	Calculated for $\text{C}_5\text{H}_8\text{N}_4\text{S}$.	Found.
N	35.89	35.94



¹ Ann. Chem. (Liebig), 331, 80 (1904).

of the 2-methylmercapto-4,6-diaminopyrimidine was evaporated twice with about 20 cc. of concentrated hydrochloric acid on the steam-bath. Methylmercaptan was evolved and the residue crystallized from water. The monohydrochloride which separated formed long, slender prisms which did not melt at 307° . This salt was dissolved in water and an excess of ammonium hydroxide was added, whereupon a fine crystalline meal was precipitated. It was difficultly soluble in hot water, and it separated as slender, rectangular, anhydrous prisms. When the material was heated it became gradually yellow at about 297° and remained a dry, yellow powder at 347° . A nitrogen determination gave :

	Calculated for $C_4H_6ON_4$.	Found.
N	44.44	44.82

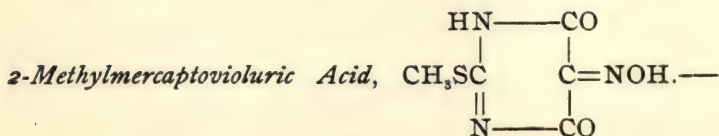
The *picrate* separated from hot water when slowly cooled in the form of thin tables. If rapidly cooled it formed bunches of slender prisms. It had a bright yellow color, and a nitrogen determination showed that it was a monopicrate :

	Calculated for $C_{10}H_9O_5N_7$.	Found.
N	27.60	27.46

It sinters at about 185° and melts with effervescence at 210° to 214° .

It was found that if the 2-methylmercapto-4,6-diaminopyrimidine was warmed with hydrochloric acid for a longer time than was sufficient to expel the mercaptan, barbituric acid was obtained. This was identified by its crystallizing with water of crystallization and by the following nitrogen determination in the dried material :

	Calculated for $C_4H_4O_2N_2$.	Found.
N	21.89	22.36



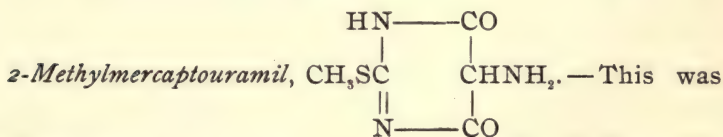
Eight grams of 2-methylmercapto-4,6-dioxypyrimidine were

dissolved in 150 cc. of water containing 2 grams of sodium hydroxide. Four grams of sodium nitrite were added and the solution was acidified with acetic acid. The solution turned dark-blue when acidified, but gradually became red. A brick-red precipitate formed after the solution stood ten hours and 4.55 grams of the isonitrosopyrimidine were obtained, or 48 per cent of the calculated. It became dark-colored when heated and gradually decomposed at 180° to 200°. The ammonium and sodium salts have a purple color. Some of the sodium salt was dissolved in warm water and acidified with hydrochloric acid. The solution became red, and, on standing, it deposited red, flat, pointed prisms, which contained 2 molecules of water of crystallization. The water was determined by heating the material at 120°.

	Calculated for $C_5H_6O_8N_3S \cdot 2H_2O$.	Found.
H_2O	11.66	11.84

A nitrogen determination in the case of the anhydrous material gave :

	Calculated for $C_5H_5O_8N_3S$.	Found.
N	22.46	22.22



obtained from the above isonitrosopyrimidine by reduction with ammonium sulphide according to Traube's method.¹ This material is difficultly soluble in water or hydrochloric acid, dilute or concentrated. It is soluble in sodium hydroxide and it is precipitated by acetic acid, in which it is difficultly soluble. A nitrogen determination gave :

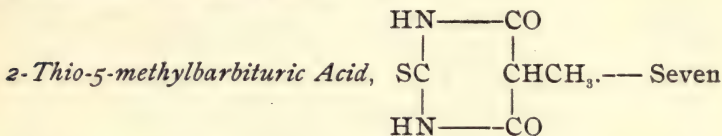
	Calculated for $C_5H_7O_2N_3S$.	Found.
N	24.28	24.37

Attempts to chlorinate this material by means of phosphorus oxychloride did not lead to a smooth result. The

¹ Ann. Chem. (Liebig), **331**, 82 (1904).

material turns brown on heating at 285° but does not melt at 301° .

The following pyrimidine derivatives were prepared by Dr. Henry F. Merriam in the course of some work on isomers of histidine. The work was interrupted by the departure of Mr. Merriam from this laboratory.



and eight-tenths grams of sodium were dissolved in alcohol and the solution added to 60 grams of methylmalonic ethyl ester. A hot alcoholic solution of 26 grams of thiourea was then added and the mixture heated gently on the steam-bath for five hours. The white sodium salt was then filtered, dissolved in a small volume of hot water, and the solution acidified strongly with hydrochloric acid. On cooling, a mass of thin plates separated. After crystallizing from water the substance melted with effervescence at about 244° . The yield was 27 grams. 2-Thio-5-methylbarbituric acid crystallizes with 1 molecule of water of crystallization, which is evolved at 120° .

	Calculated for $\text{C}_5\text{H}_6\text{O}_2\text{N}_2\text{S} \cdot \text{H}_2\text{O}$.	Found.
H_2O	18.55	18.25

A nitrogen determination in the case of the dried material gave:

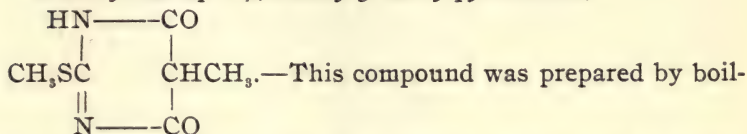
	Calculated for $\text{C}_5\text{H}_6\text{O}_2\text{N}_2\text{S}$.	Found.
N	17.72	18.04

2-Thio-5-ethylbarbituric Acid.—An alcoholic solution of 11 grams of sodium was added to 90 grams of ethylmalonic ethyl ester and a solution of 37 grams of thiourea in hot alcohol was added to the mixture, which was then warmed on the steam-bath for several hours. The white sodium salt was then removed by filtering and the free acid was liberated by means of hydrochloric acid. It separated from water in the form of long, needle-like prisms and it melted at 190° to 191° . It is

soluble in alcohol. The yield was 37 grams. It contains water of crystallization, which is given off at 120° . A nitrogen determination in the dry material gave :

	Calculated for $C_6H_8O_2N_2S$.	Found.
N	16.27	16.53

2-Methylmercapto-4,6-dioxy-5-methylpyrimidine,



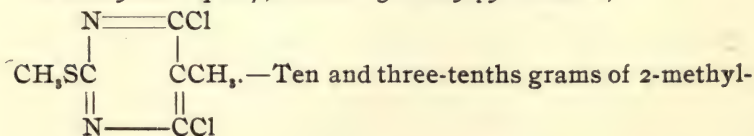
ing 2-thio-5-methylbarbituric acid with alcohol and an excess of methyl iodide. After several hours the solid material was filtered and washed with alcohol. The material was almost insoluble in water and alcohol and it was purified by crystallizing from strong acetic acid. It formed short prisms which, on heating, decomposed with effervescence at about 303° . From 28 grams of thiomethylbarbituric acid 18.5 grams of the mercapto compound were obtained.

	Calculated for $C_6H_8O_2N_2S$.	Found.
N	16.27	16.23

2-Methylmercapto-4,6-dioxy-5-ethylpyrimidine.—Thirty-six grams of 5-ethylthiobarbituric acid, treated in the same manner as the above, except that in this case, after the action was complete, most of the alcohol was evaporated and the residue was treated with water, gave 25 grams of the mercapto compound. After crystallizing from acetic acid it melted with effervescence at about 257° . It was easily soluble in alcohol and acetic acid and difficultly soluble in water. A nitrogen determination gave :

	Calculated for $C_7H_{10}O_2N_2S$.	Found.
N	15.05	15.19

2-Methylmercapto-4,6-dichlor-5-methylpyrimidine,

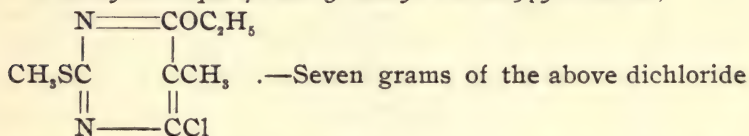


mercapto-4,6-dioxy-5-methylpyrimidine were heated on the steam-bath with 12.7 grams of phosphorus pentachloride. The material melted and, finally, the phosphorus oxychloride was removed by distilling in a vacuum. The residue was treated with ice-water and ether and the ethereal solution was dehydrated and distilled at 18 mm. pressure. The dichloride then boiled at 153° to 154°, and, on cooling, it crystallized in the form of colorless, stout prisms melting at 64°. The yield was 10.3 grams and a nitrogen determination gave :

	Calculated for $C_6H_6N_2SCl_2$.	Found.
N	13.39	13.48

As in the case of 2-methylmercapto-4,6-dichlorpyrimidine, only one chlorine atom is especially reactive in this compound.

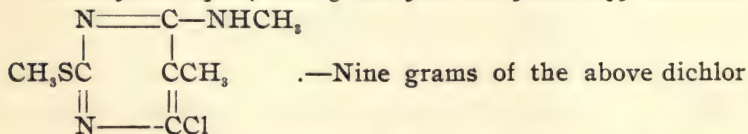
2-Methylmercapto-4-chlor-5-methyl-6-ethoxypyrimidine,



were dissolved in alcohol and 0.9 gram of sodium in alcoholic solution was added. The mixture was warmed for an hour on the steam-bath. The material was then precipitated with water and crystallized from alcohol, whereupon beautiful, colorless prisms were obtained melting at 85°. This substance is readily soluble in alcohol and benzene and insoluble in water. The yield was 6 grams. A nitrogen determination gave :

	Calculated for $C_8H_{11}ON_2SCl$.	Found.
N	12.81	13.18

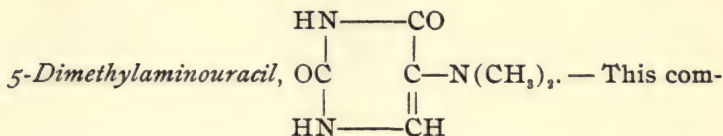
2-Methylmercapto-4-chlor-5-methyl-6-methylaminopyrimidine,



compound were heated at 145°, for three hours, with 5 grams

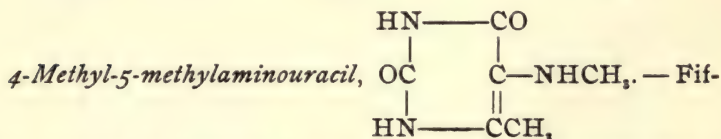
of methylamine in 58 cc. of alcohol. The solution was then evaporated, the residue washed with water and crystallized several times from alcohol. It formed stout prisms, which melted at 157° . The reaction was not complete and the yield was 5 grams. A nitrogen determination gave:

	Calculated for $C_7H_{10}N_3ClS$.	Found.
N	20.64	20.96



pound, isomeric with histidine, was prepared by heating 5-bromuracil¹ with an excess of dimethylamine at 150° for six hours. The contents of the tube were evaporated, taken up in water, and boiled with animal charcoal. The material was then crystallized from water, in which it is moderately soluble when hot, and very difficultly soluble when cold. It formed small, thin, colorless plates or films, which melted with strong effervescence at about 297° . A nitrogen determination gave:

	Calculated for $C_6H_9O_2N_3$.	Found.
N	27.09	27.23



teen grams of 4-methyl-5-bromuracil, prepared according to the directions of Behrend,² were heated for six hours at 150° with an excess of aqueous methylamine. The contents of the tube were then heated on the steam-bath until the free methylamine was removed. The bromine was removed by means of silver sulphate, the excess of silver by hydrogen sulphide, and the sulphuric acid by barium hydroxide, and the excess of the latter was precipitated by carbon dioxide. Then, on concentrating the solution to a small volume, a

¹ Wheeler and Merriam: This JOURNAL, 29, 486 (1903).

² Ann. Chem. (Liebig), 231, 249.

beautiful crop of colorless prisms separated. After crystallizing from water containing a little alcohol the compound melted at 214° . When crystallized from water, in which it is very soluble, it contains 1 molecule of water of crystallization. The presence of much alcohol in the water causes the compound to crystallize in an anhydrous condition. Water was determined by heating the material at 120° .

	Calculated for $C_6H_9O_2N_3 \cdot H_2O$.	Found.
H_2O	10.40	10.26

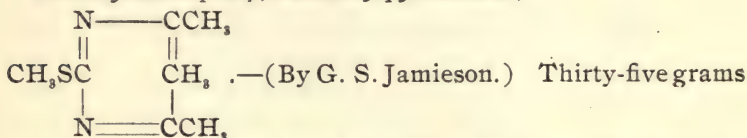
A nitrogen determination in the case of the dried material gave :

	Calculated for $C_6H_9O_2N_3$.	Found.
N	27.09	27.25

The *monohydrochloride* was prepared by dissolving the base in dilute hydrochloric acid and evaporating the solution. It formed beautiful, transparent, stout prisms, which melted at 273° with strong effervescence. The hydrochloride was less soluble in water than the free base, and the following analysis showed that the salt was anhydrous :

	Calculated for $C_6H_9O_2N_3 \cdot HCl$.	Found.
N	21.93	22.27

2-Methylmercapto-4,6-dimethylpyrimidine,



of the methyl iodide addition-product of thiourea were dissolved in 30 cc. of water containing 9 grams of potassium hydroxide and 16 grams of acetylacetone were then added. The latter dissolved when the solution was shaken vigorously for a few seconds. The clear solution gradually became turbid, and, after standing for two days, a dark-yellow oil separated. This was shaken out with ether and the ethereal solution was dehydrated over potassium hydroxide. The oil was then distilled at 28 to 29 mm. pressure, whereupon it boiled

at 135° to 137°, leaving a notable residue. Six grams of colorless, odorless oil were obtained, a yield of 24.4 per cent of the calculated. Another condensation was made with three times the above quantities and 17.7 grams of oil were obtained which boiled at 144° at 33 mm. pressure and at 123° to 125° at 14 mm. pressure. The yield in this case was 23.9 per cent of the calculated. When the oil was cooled it solidified to a white, ice-like mass and melted at about 23° to 24°. The material is moderately soluble in cold water, and when the solution is warmed the substance separates in the form of oil drops, which dissolve again on cooling. It appears to absorb moisture from the air, since only by drying over sulphuric acid could agreeing results be obtained on analysis. Nitrogen determinations then gave :

	Calculated for $C_7H_{10}N_2S$.	I.	Found. II.
N	18.18	18.22	18.32

The residue, obtained as a by-product in this preparation, was not distilled, but when crystallized from alcohol, in which it was very soluble, it separated in the form of colorless, rectangular prisms, which melted at 153° to 154° to a clear liquid. A nitrogen determination agreed with the calculated for a dicyandiamide addition-product of 2-methylmercapto-4,6-dimethylpyrimidine or an isomer. It was not further examined.

2-Oxy-4,6-dimethylpyrimidine.—The above mercapto derivative, melting at 23° to 24°, was boiled with hydrobromic acid for three hours, evaporated, taken up in water, and neutralized with alkali. It was again evaporated and the dried, powdered material was extracted with benzene containing alcohol. The extracted material was crystallized twice from water, in which it was easily soluble. It melted at 198° to 199°. Evans¹ gives the melting-point of this substance, which he prepared by a different method, at 190° to 195°. Our material was shown to be identical with that of Evans by preparing the bromine derivative melting at 145° and by its behavior with diazobenzene chloride.

NEW HAVEN, CONN., June, 1904.

¹ J. prakt. Chem., 48, 489 (1893).

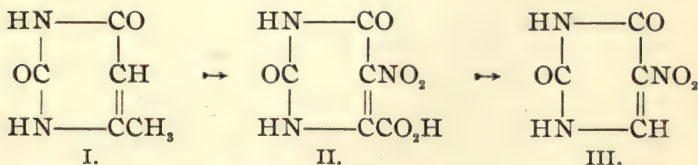
Contributions from the Sheffield Laboratory of Yale University.

CXXII. — RESEARCHES ON PYRIMIDINES: THE STRUCTURE OF SOME SUBSTITUTION- PRODUCTS.

[EIGHTH PAPER.]

BY HENRY L. WHEELER AND H. STANLEY BRISTOL.

When a pyrimidine derivative, having hydrogen both in the 4- and 5-positions, is attacked by the halogens or nitric acid, the question as to which hydrogen atom is replaced or substituted has not, hitherto, been decided. A method, which has now been successful in dealing with this question, depends on the structure of Behrend's nitro- and aminouracil. Nitro-uracil has the nitro group in the 5-position, as it is prepared from 4-methyluracil,¹ (I.), or 5-nitrouracil-4-carboxylic acid², (II.):



¹ Kohler: Ann. Chem. (Liebig), **236**, 50 (1886).

² Behrend: *Ibid.*, **229**, 36 (1885); **240**, 5 (1887).

Aminouracil results by reduction of the above nitrouracil, the amino group is, therefore, in the 5-position. Neither nitrouracil nor aminouracil has a definite melting or decomposing point. 5-Aminouracil picrate, however, has a definite effervescing point, which serves to identify it. Behrend and Grünwald¹ state that this compound melts at 147°–148°. This is incorrect, possibly a typographical error. It has been found, by several workers in this laboratory, that the action of nitric acid on uracil, 2-ethylmercapto-6-oxypyrimidine, 2-thiouracil and other pyrimidine derivatives leads to the formation of a nitrouracil. In each case, after reduction with aluminium amalgam, the product gave a picrate effervescing sharply at 247°, or 100° higher than the temperature given by the above authors. At the request of one of us, Mr. C. O. Johns prepared 5-nitrouracil (III.) by Behrends' method and this, on reduction, gave a picrate showing no signs of melting at 147° but effervesced, as in the other cases, at 247°. The compounds were identical and it therefore follows that nitric acid attacks these various pyrimidine derivatives in the 5-position.

For the purpose of comparison, Traube's 2,6-dioxy-4-aminopyrimidine or 4-aminouracil² was prepared. When the saturated aqueous solution of this substance was mixed with a saturated solution of picric acid no precipitate resulted and no picrate was obtained.

It was stated in a previous article³ that Dr. Merriam obtained 5-aminouracil when the product, obtained by brominating uracil, was heated with aqueous ammonia at 180°; it was identified by means of its picrate. A specimen of the picrate, prepared by Dr. Merriam, was found, by us, to sinter decidedly about 147°, but did not melt, or rather effervesce, until 247°. The compound proved to be identical with the above products and it therefore follows that bromine attacks uracil in the 5-position, as previously represented.

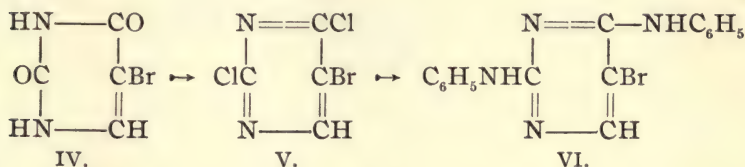
It might be expected that a 2-alkylmercapto-6-oxypyrimidine would also give a 5-brom derivative. This was proved to be the case as follows: 5-Bromuracil (IV.) was converted into

¹ Ann. Chem. (Liebig), **309**, 259 (1899).

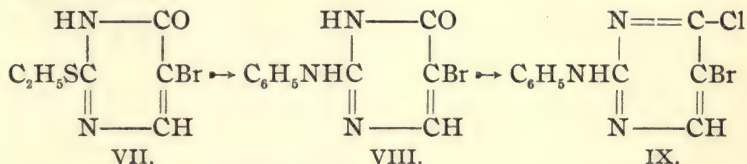
² Ber. d. chem. Ges., **33**, 1381 (1900).

³ THIS JOURNAL, **31**, 603 (1904).

2,6-dichlor-5-brompyrimidine (V.) by warming with a mixture of phosphorus oxychloride and phosphorus pentachloride and this, with aniline, gave 2,6-dianilino-5-brompyrimidine (VI.) :



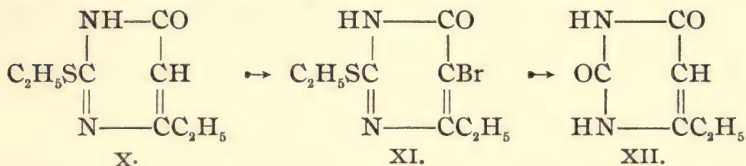
2-Ethylmercapto-6-oxypyrimidine was treated with bromine, in glacial acetic acid and the resulting brom derivative (VII.) was warmed with aniline ; this gave 2-anilino-5-brom-6-oxypyrimidine (VIII.), which was then converted into the chloride (IX.). When this chloride was warmed with aniline the product was found to be identical with the above dianilino-brompyrimidine (VI.), so that the process can be represented as follows :



Our first plan of procedure for deciding the question of the position of bromine in the mercaptooxypyrimidines, was to boil these products with hydrochloric acid and identify the brom-uracil formed. It was found, however, that prolonged boiling of 2-ethylmercapto-5-brom-6-oxypyrimidine with hydrochloric acid gave uracil, the bromine being entirely removed. The 5-brom derivatives of uracil part with their halogen more readily than those of cytosine or, in other words, an oxygen in the 6-position renders bromine in the 5-position more active than when the 6-position is occupied by an amino group. This is true not only for the replacement of bromine by hydrogen, but also by the amino group.

We have found that 2-ethylmercapto-4-ethyl-5-brom-6-oxypyrimidine (XI.) also loses bromine by simply evaporating its solution, in concentrated hydrochloric acid, to dryness on the

water-bath, the product obtained being 4-ethyluracil (XII.). The 2-ethylmercapto-4-ethyl-6-oxypyrimidine (X.) for this experiment was prepared by the condensation of the ethyl bromide addition-product of thiourea and ethylpropionylacetate, $\text{CH}_3\text{CH}_2\text{COCH}_2\text{CO.OC}_2\text{H}_5$,¹ in alkaline solution.



Bromine is represented in XI. as entering at the 5-position and not in the alkyl group. Behrend² has shown that when 4-methyluracil is brominated and then oxidized bromuracil-carboxylic acid results.

EXPERIMENTAL.

The uracil used in this work was prepared by boiling various 2-alkylmercapto-6-oxypyrimidines with concentrated hydrochloric acid. In the course of our experiments a number of new pseudoureas and alkylmercapto pyrimidines were employed. The former were prepared, for analysis, by treating pure, finely-powdered thiourea with a little alcohol and the alkyl halide was added. The mixtures were warmed on the steam-bath until solution took place and allowed to crystallize, in a vacuum, over sulphuric acid. The crystals were then simply washed with ether; they were readily soluble in water and alcohol and insoluble in benzene and ether. It was found that pseudoethylthiourea hydrobromide dissolved in acetone, it was readily soluble in pyridine and it could be crystallized from acetic anhydride.

Pseudonormalpropylthiourea hydrobromide formed long, colorless needles, which melted at about 60°.

	Calculated for $\text{C}_4\text{H}_{14}\text{N}_2\text{S.HBr.}$	Found.
N	14.07	14.19

Pseudoisobutylthiourea hydrobromide formed a fibrous mass of crystals, melting at about 96°.

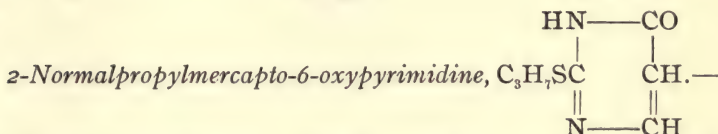
¹ Blaise : Compt. rend., 132, 978 (1901).

² Ann. Chem. (Liebig), 240, 22 (1887).

	Calculated for $C_5H_{12}N_2S \cdot HBr$.	Found.
N	13.14	13.21

Pseudoisoamylthiourea hydrobromide crystallized in long prisms, melting at about 84° .

	Calculated for $C_6H_{14}N_2S \cdot HBr$.	Found.
N	12.33	12.28



This and the following alkylmercaptooxypyrimidines were prepared by the method described in the case of the corresponding ethyl derivative.¹ The product from the condensation of 20 grams of the normalpropylbromide addition-product of thiourea, 30 grams of ethyl sodium formylacetate and 6 grams of sodium hydroxide, amounted to 12 grams. It was readily soluble in alcohol and hot water. From 40 per cent alcohol it formed long, colorless needles, melting at 117° .

	Calculated for $C_7H_{10}ON_2S$.	Found.
N	16.47	16.39

2-Isobutylmercapto-6-oxypyrimidine.—Twenty-one grams of the above pseudoisobutylthiourea hydrobromide, 38 grams of ethyl sodium formyl acetate and 4 grams of sodium hydroxide gave about 12 grams of this mercaptooxypyrimidine. When crystallized from 50 per cent alcohol it formed leaf-like plates, melting at 107° .

	Calculated for $C_8H_{12}ON_2S$.	Found.
N	15.21	15.19

2-Isoamylmercapto-6-oxypyrimidine crystallized from 50 per cent alcohol in long, thin plates, melting at 115° .

	Calculated for $C_9H_{14}ON_2S$.	Found.
N	14.14	14.08

Nitration of Uracil (By Mr. S. H. Clapp).—One gram of uracil was added to a mixture of 5 cc. of concentrated sul-

¹ THIS JOURNAL, 29, 483 (1903).

phuric acid and 10 cc. of fuming nitric acid. The mixture was heated to about 125° , in an oil-bath, for an hour. On pouring into ice-water, nitrouracil separated in colorless, prismatic needles. The yield was about 1 gram. This compound was reduced by means of aluminium amalgam, in ammoniacal solution. On filtering and concentrating, aminouracil separated in balls of needles, which were recrystallized from water; they gave 33.47 per cent of nitrogen, the calculated being 33.07.

5-Aminouracil Picrate.—The above aminouracil was dissolved in warm water and a hot solution of picric acid was added, the picrate then separated in the form of yellow, rectangular plates which began to sinter strongly at 150° , then melted, with effervescence, at 247° – 248° .

	Calculated for $C_{10}H_8O_9N_6$.	Found.
N	23.59	23.27

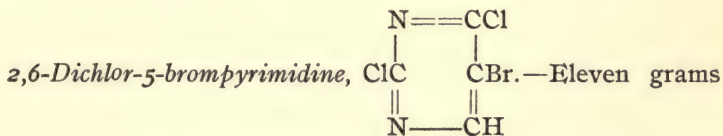
Nitration of 2-Ethylmercapto-6-oxypyrimidine.—2-Ethylmercapto-6-oxypyrimidine can be dissolved in a mixture of fuming nitric acid and concentrated sulphuric acid, at the ordinary temperature and be recovered, unaltered, on pouring into ice-water and neutralizing with sodium carbonate. If the mixture is warmed on the steam-bath until the reaction is well started, then allowed to stand in a warm place (about 60°), large crystals of nitrouracil separate.

The following was found to be the easiest method of preparing nitrouracil: Ten grams of 2-ethylmercapto-6-oxypyrimidine were dissolved in a mixture of 20 cc. of red, fuming nitric acid, 10 cc. of concentrated nitric acid and 10 cc. of concentrated sulphuric acid. The reaction was started by warming on the steam-bath, then the liquid was allowed to stand, at about 60° , for several hours, 4.9 grams of well-crystallized nitrouracil separated. The crystals were filtered and the acid filtrate allowed to stand for 24 hours longer, at 60° , whereupon 2.7 grams of nitrouracil separated, or 7.6 grams in all. This is a yield of 75.5 per cent of the calculated. When the compound was reduced by means of aluminium amalgam and the picrate prepared, it was found that the latter became

black at about 190° , but nevertheless effervesced sharply at 247° . The same partial decomposition and effervescing point was noticed in the case of the picrate prepared in the following experiment.

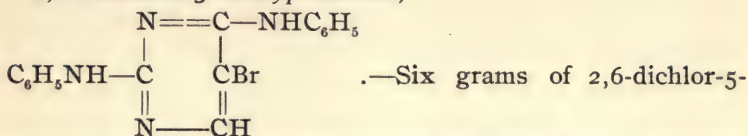
Nitration of 2-Thio-6-oxypyrimidine.—Twenty-five per cent nitric acid reacts energetically with this pyrimidine derivative and a portion is converted into nitrouracil. Eight grams of 2-thiouracil gave about 4 grams nitrouracil; beside this a far more soluble substance was formed, which gave a bulky precipitate with mercuric chloride, it was probably 6-oxypyrimidine, but was not isolated.

Nitration of 2-Ethylmercapto-6-chlorpyrimidine (By Dr. T. B. Johnson).—The mercaptochlorpyrimidine (1.5 grams) was added to a mixture of 4 cc. of concentrated nitric acid and 4 cc. of concentrated sulphuric acid. The temperature of the mixture was not allowed to rise above 90° ; it was maintained at this point until effervescence ceased. The product was cooled, poured on to ice and crystallized from water; it contained 27.1 per cent nitrogen, the calculated percentage for nitrouracil is 26.7. This substance was reduced and the picrate prepared; it melted or effervesced at 247° .



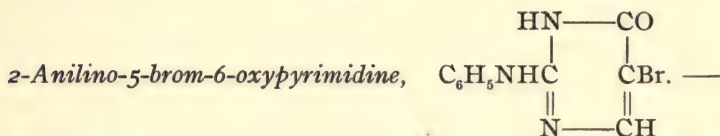
of 5-bromuracil, 13 grams of phosphorus pentachloride and 40 cc. of phosphorus oxychloride were mixed and warmed on the steam-bath. Hydrogen chloride was evolved and, after 4 days, all of the bromuracil dissolved. The solution was poured on to ice and extracted with ether. The ether was dried over calcium chloride and evaporated, leaving 8 grams of oil, which boiled at 119° – 120° (17–18 mm.). It solidified, in a freezing-mixture, to a crystalline mass and melted at -3° – -2° .

	Calculated for $\text{C}_4\text{HN}_2\text{Cl}_2\text{Br}$.	Found.
N	12.28	12.46

2,6-Dianilino-5-bromypyrimidine,

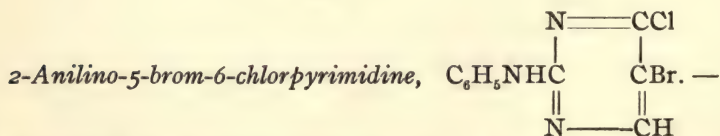
bromypyrimidine were mixed with 10 grams of aniline, heat was evolved and the mass solidified to a hard cake. This was powdered and boiled with benzene, the benzene and aniline were removed by a current of steam and the insoluble material was crystallized from alcohol. It formed a felted mass of colorless needles, difficultly soluble in water, which melted to a clear oil at 191° .

	Calculated for $\text{C}_{10}\text{H}_{13}\text{N}_4\text{Br}$.	Found.
N	16.42	16.42



Five grams of 2-ethylmercapto-5-brom-6-oxypyrimidine were heated with excess of aniline on the steam-bath, until the odor of mercaptan disappeared (24 hours). At first solution took place, then crystalline material separated. The product, after washing with cold alcohol, was free from sulphur and weighed about 6 grams. It was difficultly soluble in water, alcohol, benzene and acetone. From alcohol it separated in the form of colorless, needle-like prisms, melting at 246° with effervescence.

	Calculated for $\text{C}_{10}\text{H}_8\text{ON}_2\text{Br}$.	Found.
N	15.78	16.11

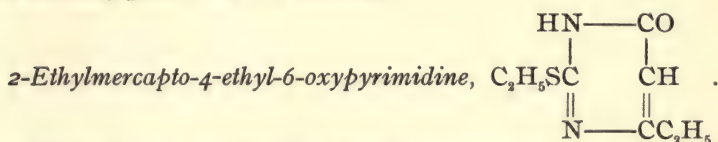


The above anilinobromoxypyrimidine (4.7 grams) was digested on the steam-bath with phosphorus oxychloride until solution took place and hydrogen chloride ceased being

evolved. It was then poured on to ice and the solid that separated was extracted with ether. It was readily soluble in ether and benzene and crystallized from ligroin in bunches of long, radiating, colorless needles which melted, to a clear oil, at 106° – 107° .

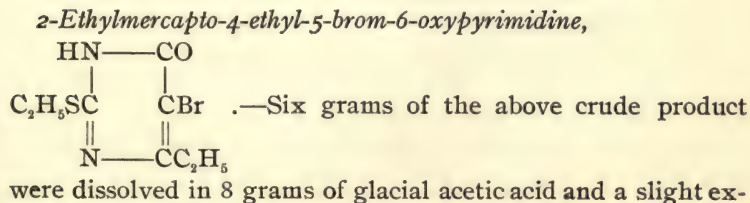
N	Calculated for	Found.
	$C_{10}H_7N_3ClBr$.	
	14.76	14.45

A small quantity of this compound was warmed with excess of aniline on the steam-bath, the mixture liquefied and in a few minutes solidified to a hard cake. On crystallizing from alcohol it gave a felted mass of needles, melting at 191° and, when mixed with 2,6-dianilino-5-brompyrimidine, described above, the melting-point was not altered.



—A solution of 5.7 grams of sodium hydroxide, 12.5 grams of pseudoethylthiourea hydrobromide and 10 grams of ethyl propionyl acetate was made in 25 cc. of water, the constituents being added in the order named. The mixture was allowed to stand for a number of hours, then warmed and, on cooling, it was acidified with acetic acid. An oil separated which finally solidified, and, after washing and drying, weighed about 6 grams. It dissolved, with difficulty, in hot water, giving colorless, truncated pyramids. From alcohol, in which it is very soluble, it crystallized in large, stout, transparent prisms, which melted at 89° without decomposition.

N	Calculated for	Found.
	$C_8H_{12}ON_2S$.	
	15.21	15.13



cess of bromine added. A mass of six-sided plates separated and more was obtained on diluting with water. The yield of crude material was a little over 6 grams. When crystallized from alcohol it formed large, stout, colorless, transparent prisms and melted, to a clear liquid, at 172° – 173° .5.

	Calculated for $C_8H_{11}ON_2SBr$.	Found.
N	10.64	10.64
$ \begin{array}{c} \text{HN} \text{---} \text{CO} \\ \qquad \\ \text{OC} \qquad \text{CH} \\ \qquad \\ \text{HN} \text{---} \text{CC}_2\text{H}_5 \end{array} $		
4-Ethyluracil,	.—The above mercaptobrom-	

pyrimidine dissolves in concentrated hydrochloric acid but is precipitated again by adding water. It was digested on the steam-bath, with strong hydrochloric acid, for some time and then evaporated to dryness. The residue was more readily soluble in water than in alcohol. When crystallized from the latter it formed beautiful, colorless tables or blocks, which melted at 204° to a clear liquid; it effervesced at about 270° .

	Calculated for $C_6H_8O_2N_2$.	Found.
N	20.0	20.2

The same product was obtained by boiling 2-ethylmercapto-4-ethyl-6-oxypyrimidine, melting at 89° , with hydrochloric acid.

$$\begin{array}{c}
 \text{HN} \text{---} \text{CO} \\
 | \qquad | \\
 \text{OC} \qquad \text{CBr} \\
 | \qquad || \\
 \text{HN} \text{---} \text{CC}_2\text{H}_5
 \end{array}$$

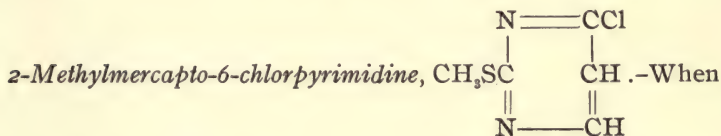
4-Ethyl-5-bromuracil, .—The above 4-ethyl-

uracil was dissolved in glacial acetic acid, in which it is not very soluble and a slight excess of bromine was added. On cooling, very thin, oblong plates separated. These were difficultly soluble in hot water and crystallized, when slowly cooled, in long, thin, snow-white, glistening prisms that were highly etched. The material crystallized from alcohol in plates, or from strong solution in wisps. At 230° – 231° it melted to a yellow liquid, which immediately turned brown and then effervesced.

	Calculated for $C_6H_7O_2N_2Br$.	Found.
N	12.78	12.62

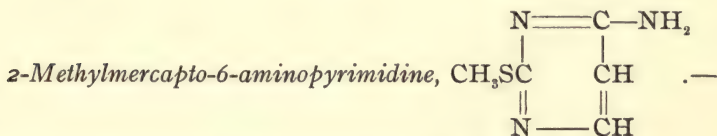
2-Methylmercapto-6-oxypyrimidine Hydrochloride.—This was obtained on passing chlorine into a glacial acetic acid solution of the mercaptopyrimidine and precipitating with ether. It was crystallized from glacial acetic acid and formed prismatic plates, which were washed with ether. It was very soluble in alcohol and water, the aqueous solution giving a strong odor of mercaptan. When boiled with hydrochloric acid, uracil was obtained. It melted, with vigorous effervescence, at 189° .

	Calculated for $C_5H_6ON_2S.HCl$.	Found.
N	15.7	15.8



the above hydrochloride (32 grams) was warmed with the calculated quantity of phosphorus pentachloride and some phosphorus oxychloride, it dissolved and hydrogen chloride was given off. The solution was poured on to ice and extracted with ether, dried and distilled (36 mm.). The colorless oil boiled, for the most part, at 139° – 140° ; on cooling in a freezing mixture it solidified and melted at about -2° – 0° .

	Calculated for $C_6H_5N_2SCl$.	Found.
N	17.4	16.9



The above chloride was heated with a large excess of concentrated alcoholic ammonia, at 120° – 130° , for 3 hours. The ammonium chloride that separated was filtered and the filtrate evaporated to dryness. The residue was treated with water, dried and crystallized from benzene. It formed large, colorless, diamond-shaped, prismatic plates which melted, to a clear oil, at 125° –

126°. It was readily soluble in alcohol and acetone, insoluble in ether and ligroin.

	Calculated for $C_5H_7N_8S$.	Found.
N	29.79	29.76
NEW HAVEN, CONN., January, 1905.		

Contributions from the Sheffield Laboratory of Yale University.

CXXIII. — RESEARCHES ON PYRIMIDINES: THE
ACTION OF POTASSIUM THIOCYANATE
UPON SOME IMIDE CHLORIDES.

[NINTH PAPER.]

BY HENRY L. WHEELER AND H. STANLEY BRISTOL.

No attention has hitherto been given to the action of potassium thiocyanate upon imide chlorides. It was, therefore, impossible to predict whether normal thiocyanates, RSCN , or isothiocyanates, mustard oils, RNCS , would be formed. Most alkyl halides give normal thiocyanates, while the acyl halides give isothiocyanates. Imide chlorides, $-\text{C} \begin{array}{l} \text{N}- \\ \text{Cl} \end{array}$, are

more closely related to acyl halides, $-\text{C} \begin{array}{l} \text{O} \\ \text{Cl} \end{array}$, than to the alkyl halides and, in the pyrimidine series, the compounds contain the grouping $\text{C}=\text{C}-\text{CCl}$,¹ therefore isothiocyanates might be expected to be formed in this reaction. This being the case, facilities for further syntheses would be increased.

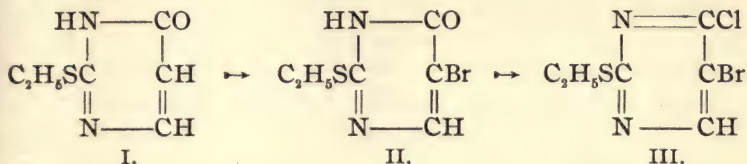
We have investigated this reaction in the case of 2-ethylmercapto-6-chlorpyrimidine, 2-ethylmercapto-5-brom-6-chlorpyrimidine and 2-ethylmercapto-5-methyl-6-chlorpyrimidine and we find, in each instance, that the chlorides give isothiocyanates.

The preparation of derivatives has been more thoroughly carried out in the case of 2-ethylmercapto-5-brom-6-chlorpyrimidine, III., than with the other chlorides. This was prepared, as already shown,² from 2-ethylmercapto-6-oxypyrim-

¹ Compare Wheeler and Jamieson : J. Am. Chem. Soc., **24**, 746 (1902).

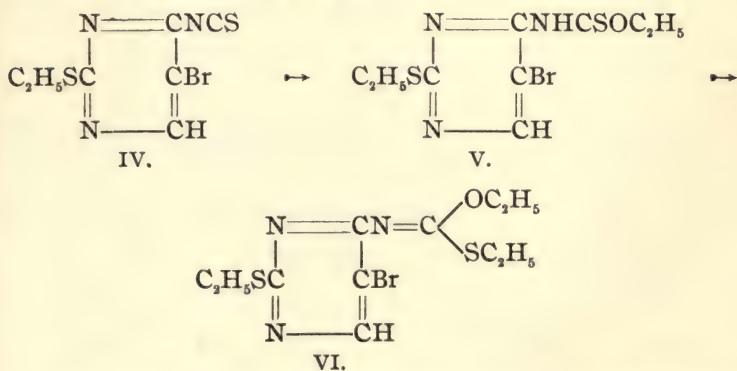
² Wheeler and Johnson : THIS JOURNAL, **31**, 603 (1904).

idine (I.) by brominating (II.), then chlorinating in the 6-position.



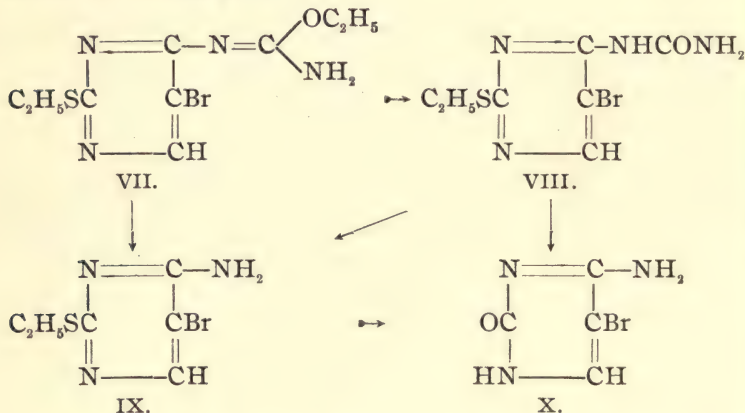
When 2-ethylmercapto-5-brom-6-chlorpyrimidine was boiled, in toluene solution, with potassium thiocyanate, 2-ethylmercapto-5-brom-6-isothiocyanpyrimidine (IV.) was obtained. This reacted with ammonia, aniline, etc., yielding the corresponding thiourea derivatives.

When, however, the chlorbrommercaptopyrimidine (III.) was boiled with an alcoholic solution of potassium thiocyanate, the thionurethane (V.) was obtained and this compound, with sodium ethylate and ethyl bromide, gave the imidothiocarbonic ester represented by Formula VI.



When this imidothiocarbonic ester derivative was treated with alcoholic ammonia, it evolved mercaptan and the pseudo-oxygen urea (VII.) was formed smoothly. This gave the normal urea (VIII.) when treated with cold, concentrated hydrochloric acid. Boiling hydrochloric acid then gave 5-bromcytosine (X.). Attempts to condense the pseudooxygen urea, or the normal urea, to a purin derivative were without success. The bromine in these compounds is firmly bound but the urea and pseudourea groups are easily removed.

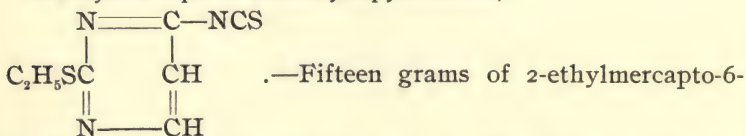
When the pseudourea (VII.) was heated with pyridine or aqueous ammonia, in a closed tube, 2-ethylmercapto-5-brom-6-aminopyrimidine was formed (IX.). The same result was obtained when the compound was boiled with formic acid. Sodium, in boiling benzene, failed to remove bromine but attacked the pseudourea grouping. 2-Ethylmercapto-5-brom-6-aminopyrimidine was also obtained when the normal urea was heated above its melting-point.



In the latter part of this article some new uracil and cytosine derivatives are described.

EXPERIMENTAL.

2-Ethylmercapto-6-isothiocyanpyrimidine,



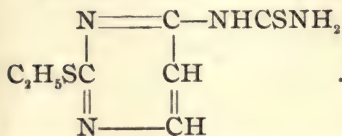
chlorpyrimidine,¹ boiling at 135° (24 mm.) and at 128° (16 mm.) were dissolved in 20 cc. of toluene and 25 grams of dry, powdered potassium thiocyanate were added. The mixture was boiled, in a paraffin-bath, for 12 hours. The insoluble salts were then removed by filtering, the toluene was evaporated and the residue distilled under reduced pressure. It boiled, for the most part, at 180° (32 mm.). The distillate solidified

¹ Wheeler and Johnson: THIS JOURNAL, 29, 497 (1903); 31, 596 (1904).

and, when crystallized from benzene, it separated in small, light-yellow, prismatic plates and melted, on slowly heating, at 175°.

	Calculated for $C_7H_7N_3S_2$.	Found.
N	21.32	21.53

2-Ethylmercapto-6-thioureapyrimidine,



—On adding concentrated aqueous

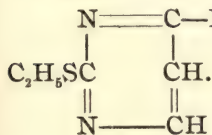
ammonia to a portion of the above toluene solution containing the isothiocyanate, an energetic reaction took place, with evolution of heat and a solid mass separated. When this material was crystallized from alcohol it formed long, thin, colorless prisms and melted at 214°. It was difficultly soluble in water.

	Calculated for $C_7H_{10}N_4S_2$.	Found.
N	26.17	25.83

2-Ethylmercapto-6-phenylthioureapyrimidine was prepared by adding aniline to a toluene solution of the pure crystallized isothiocyanate. A solid separated, with evolution of heat and, when crystallized from alcohol, it formed a felted mass of long, colorless needles resembling cotton. It was almost insoluble in hot water and fairly soluble in hot alcohol, it melted at 205°.

	Calculated for $C_{13}H_{14}N_4S_2$.	Found.
N	19.31	19.10

2-Ethylmercapto-6-thionethylurethane pyrimidine,



—When 5 grams of 2-ethyl-

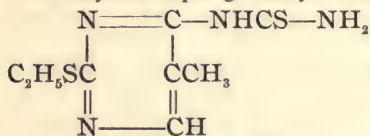
mercapto-6-chlorpyrimidine were added to an alcoholic solution of 2.8 grams of potassium thiocyanate, potassium chloride separated almost at once. The mixture was warmed on the water-bath for 3 hours, the alcohol was then evaporated and the residue treated with water. The crude product weighed 6

grams and, when crystallized from alcohol, it formed long, thin, light-yellow, etched plates, melting at 93° . It is readily soluble in hot alcohol and difficultly soluble in cold.

	Calculated for $C_9H_{13}ON_3S_2$.	Found.
N	17.28	16.89

When this urethane was boiled with concentrated hydrochloric acid, until mercaptan ceased being evolved and then evaporated, a mixture of about equal quantities of uracil and cytosine was obtained.

2-Ethylmercapto-5-methyl-6-thioureapyrimidine,

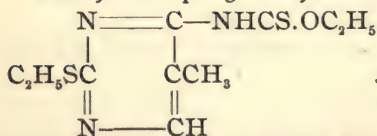


—Eleven grams of 2-ethylmer-

capto-5-methyl-6-chlorpyrimidine, 30 grams of dry, finely powdered potassium thiocyanate and 30 cc. of toluene were mixed and boiled for 7 hours, in an oil-bath. The potassium thiocyanate was added, in portions of 10 grams, from time to time. The mixture was filtered and, to a portion of the solution, alcoholic ammonia was added, the thioureapyrimidine then separated in a fairly pure state. It was moderately soluble in hot alcohol and benzene, difficultly soluble in cold and crystallized from benzene in bunches of radiating needles. It was difficultly soluble in hot water and melted, to a clear oil, at 192° .

	Calculated for $C_8H_{12}N_4S_2$.	Found.
N	24.56	24.30

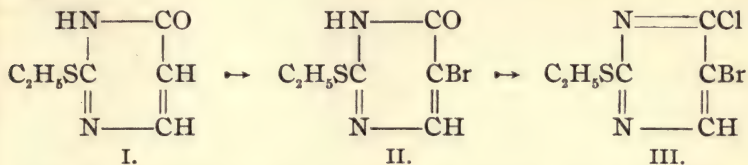
2-Ethylmercapto-5-methyl-6-thionurethane pyrimidine,



—Ten grams of the chloride

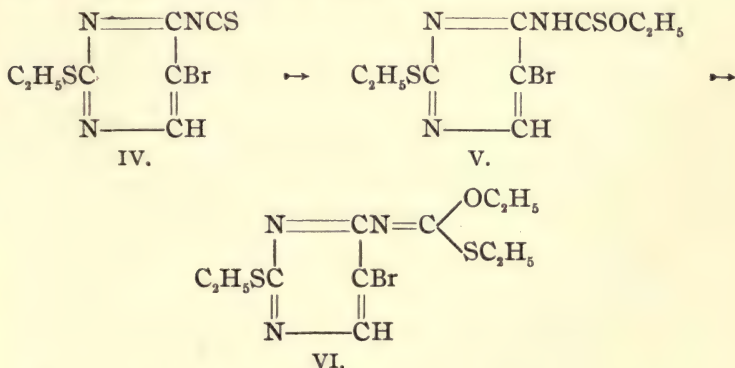
were boiled with 15 grams of dry, finely powdered potassium thiocyanate, in toluene, for 15 hours. Then an excess of alcohol was added and the mixture boiled again for 6 hours. The solution was filtered hot and evaporated to dryness, the residue

idine (I.) by brominating (II.), then chlorinating in the 6-position.



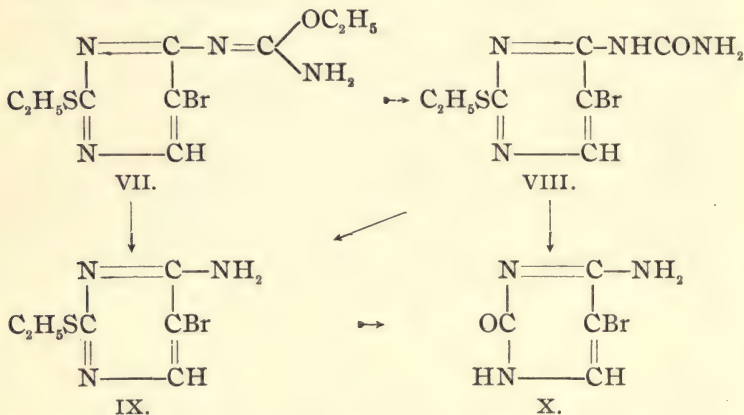
When 2-ethylmercapto-5-brom-6-chlorpyrimidine was boiled, in toluene solution, with potassium thiocyanate, 2-ethylmercapto-5-brom-6-isothiocyanyrimidine (IV.) was obtained. This reacted with ammonia, aniline, etc., yielding the corresponding thiourea derivatives.

When, however, the chlorbrommercaptopyrimidine (III.) was boiled with an alcoholic solution of potassium thiocyanate, the thionurethane (V.) was obtained and this compound, with sodium ethylate and ethyl bromide, gave the imidothiocarbonic ester represented by Formula VI.



When this imidothiocarbonic ester derivative was treated with alcoholic ammonia, it evolved mercaptan and the pseudo-oxygen urea (VII.) was formed smoothly. This gave the normal urea (VIII.) when treated with cold, concentrated hydrochloric acid. Boiling hydrochloric acid then gave 5-bromcytosine (X.). Attempts to condense the pseudooxygen urea, or the normal urea, to a purin derivative were without success. The bromine in these compounds is firmly bound but the urea and pseudourea groups are easily removed.

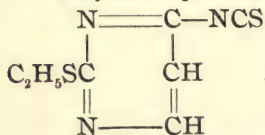
When the pseudourea (VII.) was heated with pyridine or aqueous ammonia, in a closed tube, 2-ethylmercapto-5-brom-6-aminopyrimidine was formed (IX.). The same result was obtained when the compound was boiled with formic acid. Sodium, in boiling benzene, failed to remove bromine but attacked the pseudourea grouping. 2-Ethylmercapto-5-brom-6-aminopyrimidine was also obtained when the normal urea was heated above its melting-point.



In the latter part of this article some new uracil and cytosine derivatives are described.

EXPERIMENTAL.

2-Ethylmercapto-6-isothiocyanpyrimidine,



.—Fifteen grams of 2-ethylmercapto-6-

chlorpyrimidine,¹ boiling at 135° (24 mm.) and at 128° (16 mm.) were dissolved in 20 cc. of toluene and 25 grams of dry, powdered potassium thiocyanate were added. The mixture was boiled, in a paraffin-bath, for 12 hours. The insoluble salts were then removed by filtering, the toluene was evaporated and the residue distilled under reduced pressure. It boiled, for the most part, at 180° (32 mm.). The distillate solidified

¹ Wheeler and Johnson: THIS JOURNAL, 29, 497 (1903); 31, 596 (1904).

and, when crystallized from benzene, it separated in small, light-yellow, prismatic plates and melted, on slowly heating, at 175°.

Calculated for
C₇H₇N₃S₂.

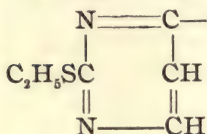
Found.

N

21.32

21.53

2-Ethylmercapto-6-thiourea-pyrimidine,



.—On adding concentrated aqueous

ammonia to a portion of the above toluene solution containing the isothiocyanate, an energetic reaction took place, with evolution of heat and a solid mass separated. When this material was crystallized from alcohol it formed long, thin, colorless prisms and melted at 214°. It was difficultly soluble in water.

Calculated for
C₇H₁₀N₄S₂.

Found.

N

26.17

25.83

2-Ethylmercapto-6-phenylthiourea-pyrimidine was prepared by adding aniline to a toluene solution of the pure crystallized isothiocyanate. A solid separated, with evolution of heat and, when crystallized from alcohol, it formed a felted mass of long, colorless needles resembling cotton. It was almost insoluble in hot water and fairly soluble in hot alcohol, it melted at 205°.

Calculated for
C₁₃H₁₄N₄S₂.

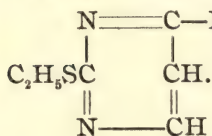
Found.

N

19.31

19.10

2-Ethylmercapto-6-thionethylurethane-pyrimidine,



.—When 5 grams of 2-ethyl-

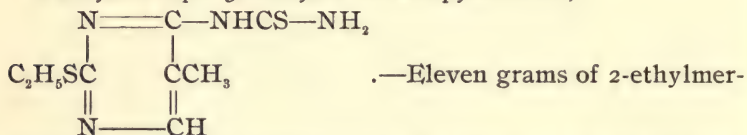
mercapto-6-chlorpyrimidine were added to an alcoholic solution of 2.8 grams of potassium thiocyanate, potassium chloride separated almost at once. The mixture was warmed on the water-bath for 3 hours, the alcohol was then evaporated and the residue treated with water. The crude product weighed 6

grams and, when crystallized from alcohol, it formed long, thin, light-yellow, etched plates, melting at 93° . It is readily soluble in hot alcohol and difficultly soluble in cold.

	Calculated for $C_9H_{13}ON_3S_2$.	Found.
N	17.28	16.89

When this urethane was boiled with concentrated hydrochloric acid, until mercaptan ceased being evolved and then evaporated, a mixture of about equal quantities of uracil and cytosine was obtained.

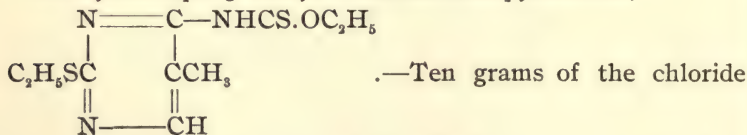
2-Ethylmercapto-5-methyl-6-thioureaprimidine,



capto-5-methyl-6-chlorpyrimidine, 30 grams of dry, finely powdered potassium thiocyanate and 30 cc. of toluene were mixed and boiled for 7 hours, in an oil-bath. The potassium thiocyanate was added, in portions of 10 grams, from time to time. The mixture was filtered and, to a portion of the solution, alcoholic ammonia was added, the thioureaprimidine then separated in a fairly pure state. It was moderately soluble in hot alcohol and benzene, difficultly soluble in cold and crystallized from benzene in bunches of radiating needles. It was difficultly soluble in hot water and melted, to a clear oil, at 192° .

	Calculated for $C_8H_{12}N_4S_2$.	Found.
N	24.56	24.30

2-Ethylmercapto-5-methyl-6-thionurethaneprimidine,



were boiled with 15 grams of dry, finely powdered potassium thiocyanate, in toluene, for 15 hours. Then an excess of alcohol was added and the mixture boiled again for 6 hours. The solution was filtered hot and evaporated to dryness, the residue

treated with water and filtered. It was then taken up in alkali and extracted with ether, the alkaline solution acidified with acetic acid and the pasty, semi-solid precipitate filtered. This was dissolved in ether and dried with potassium carbonate. On evaporation an oil was obtained which solidified completely only after standing 9 months. It was purified by dissolving in benzene and precipitating with ligroin, whereupon groups of pale-yellow prisms separated. It melted at 88° – 89° , to a clear oil. It was readily soluble in alcohol, ether and benzene and difficultly soluble in water.

N	Calculated for $C_{10}H_{16}ON_3S_2$.	Found.
	16.34	16.71
$ \begin{array}{c} \text{N}=\text{CNCS} \\ \qquad \qquad \\ \text{C}_2\text{H}_5\text{SC} \qquad \text{CBr} \\ \qquad \qquad \\ \text{N}=\text{CH} \end{array} $		
2-Ethylmercapto-5-brom-6-isothiocyanypyrimidine, — The 2-ethylmercapto-5-brom-6-chlor-		

pyrimidine, used as the starting-point for the following experiments, was described in a previous paper,¹ but the boiling-point of the material was not given. It was observed to boil at 168° (24–25 mm.) and at 179° – 180° (36 mm.). Fifteen gram portions of the chloride were dissolved in 30 cc. of toluene and 30 grams of finely pulverized, dry potassium thiocyanate were added, in portions of 10 grams each, from time to time. The mixture was boiled for 9 hours, in an oil-bath. It was then filtered and the toluene mostly removed by evaporating on the water-bath, under diminished pressure. Petroleum ether was now added, in slight amount, enough to separate an oily substance. The solutions were quickly poured off from this through a filter and, on standing, beautiful, small, pale-yellow prisms formed, which were purified by dissolving in toluene and adding a small amount of petroleum ether. The material was readily soluble in benzene and toluene and difficultly soluble in petroleum ether. It melted at 79° – 80° .

N	Calculated for $C_7H_6N_3S_2Br$.	Found.
	15.21	15.45

¹ Wheeler and Johnson: THIS JOURNAL, 31, 603 (1904).

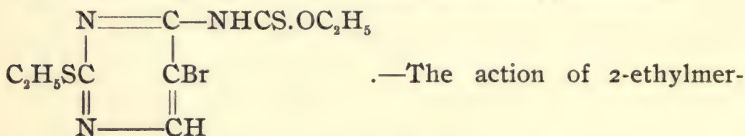
2-Ethylmercapto-5-brom-6-thioureapyrimidine.—A portion of the toluene solution of the isothiocyanate was mixed with alcoholic ammonia in excess. Heat was evolved and the thiourea separated at once. It was found to be difficultly soluble in water and alcohol and more soluble in benzene, from which it crystallized in light-yellow plates, melting at 220° .

	Calculated for $C_7H_9N_4S_2Br$.	Found.
N	19.11	18.96

2-Ethylmercapto-5-brom-6-phenylthioureapyrimidine.—Aniline acted at once, with evolution of heat, on the isothiocyanate. The product was difficultly soluble in water, fairly soluble in benzene, it separated from alcohol in the form of a felted mass of fine, colorless needles, which melted at 166° – 167° .

	Calculated for $C_{13}H_{13}N_4S_2Br$.	Found.
N	15.17	15.03

2-Ethylmercapto-5-brom-6-thionethylurethane pyrimidine,



capto-5-brom-6-chlorpyrimidine on potassium thiocyanate, in alcoholic solution, was not smooth. In addition to the thionurethane, two other compounds were isolated as products of the reaction. These were 2-ethylmercapto-5-brom-6-thiopyrimidine and 2-ethylmercapto-5-brom-6-aminopyrimidine.

Thirty-three grams of 2-ethylmercapto-5-brom-6-chlorpyrimidine were added to a concentrated solution of 20 grams of potassium thiocyanate in alcohol and the mixture was boiled for several hours. At the end of this operation the odor of ethylthiocyanate was noticed. The solution was filtered and the alcohol evaporated. The residue was treated with cold benzene and filtered, leaving 2-ethylmercapto-5-brom-6-thiopyrimidine and potassium thiocyanate undissolved. The benzene was then evaporated and the residue treated with dilute sodium hydroxide and extracted with ether. The ether solution con-

tained the 2-ethylmercapto-5-brom-6-aminopyrimidine, melting at 124°, which was described in a previous paper.¹

The urethane was precipitated from the alkaline solution by means of acetic acid; the yield of crude material was 25 grams. It was readily soluble in hot alcohol, difficultly soluble in cold and formed long, pointed, light-yellow, prismatic plates, melting at 82°.

In two other experiments 18.5 grams of the chloride gave 13 grams of the urethane and 15 grams of the chloride gave 11.5 grams of the urethane.

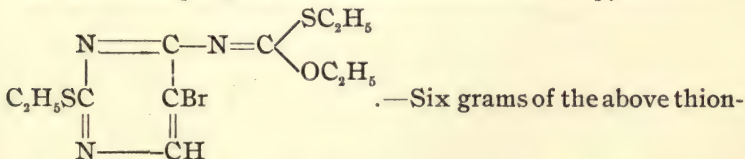
N	Calculated for $C_9H_{12}ON_2S_2Br$.	Found.
	13.04	12.97
$ \begin{array}{c} \text{HN} \text{---} \text{CS} \\ \qquad \\ \text{C}_2\text{H}_5\text{SC} \quad \text{CBr.} \\ \qquad \\ \text{N} \text{---} \text{CH} \end{array} $		

—The residue, left undissolved by cold benzene, in the above preparation was washed with water, dried and crystallized from benzene. It formed pointed, etched, pale-yellow plates and melted, with slight effervescence, at 198°.

N	Calculated for $C_9H_7N_2S_2Br$.	Found.
	11.15	11.04

In the course of some other work Mr. S. H. Clapp prepared this compound, by the action of potassium hydrosulphide on 2-ethylmercapto-5-brom-6-chlorpyrimidine. When this preparation was mixed with the above the melting-point was not altered.

2-Ethylmercapto-5-brom-6-iminothioethylcarbonatepyrimidine,



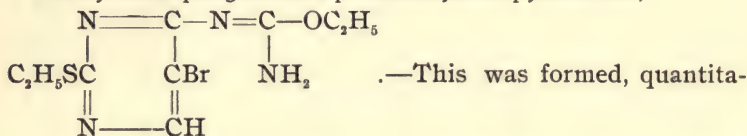
ethylurethane were dissolved in a solution of 0.42 gram of sodium, in a small quantity of absolute alcohol and then 4 grams

¹ THIS JOURNAL, 31, 604 (1904).

of ethyl bromide were added. On standing a short time sodium bromide separated. The mixture was warmed on the steam-bath, then filtered and evaporated to dryness. The product was treated with ether, filtered from sodium bromide and evaporated. The residue, on cooling, solidified. The yield was found to be 6 grams. The product was purified by crystallizing from alcohol containing a little water. It then formed long, colorless prisms, melting at 43° , which were readily soluble in alcohol, ether and warm ligroin but insoluble in water.

	Calculated for $C_{11}H_{16}ON_8S_2Br$.	Found.
N	12.00	11.87

2-Ethylmercapto-5-brom-6-pseudoethylureaprimidine,



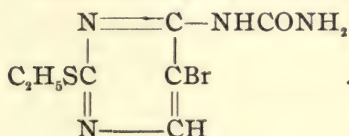
tively, by passing ammonia gas into an alcoholic solution of the above aminothioethylcarbonate. It crystallized from alcohol in beautiful, long needles, which developed into thin plates, melting at 110° and decomposing about 230° , forming a tarry mass on cooling. It was difficultly soluble in hot water and insoluble in cold, dissolved readily in cold benzene and warm alcohol. It was insoluble in alkali and soluble in hydrochloric acid.

	Calculated for $C_9H_{13}ON_4SBr$.	Found.
N	18.3	18.1

This material can be boiled with pyridine (3 hours) or dimethyl aniline (10 minutes) and recovered unaltered. No bromine is removed under these conditions. When heated with pyridine at 180° – 190° , in a closed tube, for 5 hours, the only crystalline substance obtained was 2-ethylmercapto-5-brom-6-aminopyrimidine. This substance was also obtained when the material was boiled with formic acid. A nitrogen determination gave 17.7 per cent, while the calculated is 17.9 per cent. The action of concentrated aqueous ammonia, in a closed tube, first at 90° for 3 hours, then at 145° – 150° for $4\frac{1}{2}$

hours, gave the same result. The hydrochloride of this base was obtained when the pseudourea was warmed, for a short time, with concentrated hydrochloric acid. About 0.5 gram of the pseudourea was dissolved in benzene and treated with an excess of sodium, the mixture was boiled for 12 hours. The metal became coated with a thick deposit and, on filtering and evaporating the benzene, there was no residue. The sodium and coating was treated with alcohol and a portion was acidified with nitric acid, whereupon silver nitrate gave no insoluble precipitate, and, therefore, no bromine had been removed. On acidifying the alkaline solution with acetic acid and evaporating, a substance was obtained melting at 287° , with effervescence. On dissolving in acetone and precipitating with ether it effervesced at 310° . It was concluded that this material was *2-ethylmercapto-5-brom-6-cyanamidepyrimidine*, not only from its mode of formation, but also because, on warming with dilute hydrochloric acid, it gave the following urea derivative :

2-Ethylmercapto-5-brom-6-ureaprimidine,



.—This was also produced by al-

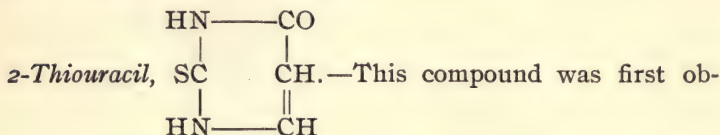
lowing the above pseudourea to stand dissolved in cold concentrated hydrochloric acid. After several days the urea separated on adding water. It crystallized from alcohol in short, pointed plates which, on long standing, developed into stout prisms and melted, when slowly heated, at 167° .

	Calculated for $\text{C}_7\text{H}_9\text{ON}_4\text{SBr}$.	Found.
N	20.2	19.8

If this material is heated to its melting-point, cooled and reheated, it melts unaltered. If the heating is continued a little above its melting-point it slowly becomes semi-solid. One gram of the urea derivative was heated, in a test-tube, at 170° – 180° , a portion sublimed, crystallizing in prismatic plates in the cool part of the tube. This melted at 124° and, when

mixed with some 2-ethylmercapto-5-brom-6-aminopyrimidine, the melting-point was not altered.

When this urea was boiled with concentrated hydrochloric acid 5-bromcytosine¹ was obtained.



tained, along with 2-ethylmercapto-6-oxypyrimidine, when pseudoethylthiourea, containing some thiourea, was condensed with ethyl sodium formylacetate. A concentrated aqueous solution of 150 grams of ethyl sodium formylacetate was mixed with a saturated solution of 50 grams of thiourea. The mixture was then warmed on the steam-bath for a short time, cooled and the deep red solution was precipitated with a slight excess of acetic acid. A yellowish-white, granular precipitate separated, weighing 50 grams. This crystallized from alcohol or water in colorless prisms. It is difficultly soluble in these solvents. When heated, it effervesces above 300°.

	Calculated for $\text{C}_4\text{H}_4\text{ON}_2\text{S}$.	Found.
N	21.8	21.9

2-Ethylmercapto-6-anilinopyrimidine hydrochloride was prepared by mixing 2-ethylmercapto-6-chlorpyrimidine (10 grams) with aniline (5.3 grams), after standing over night, then warming on the water-bath for several hours, the mixture solidified. It was readily soluble in hot alcohol and hot water and crystallized in the form of colorless needles or prisms. It melted at 198° with effervescence.

	Calculated for $\text{C}_{12}\text{H}_{14}\text{N}_3\text{S}\text{Cl}$.	Found.
N	15.7	15.9

When this hydrochloride was dissolved in hot water and precipitated with ammonia, an oil separated. This finally solidified and was purified by repeatedly dissolving in alcohol and precipitating with water. The base is very soluble in alcohol. It formed fine, colorless needles and melted at 68°.

¹ THIS JOURNAL, 31, 604 (1904).

	Calculated for $C_{12}H_{13}N_3S$.	Found.
N	18.1	18.2

2-Oxy-6-anilinopyrimidine (*Phenylcytosine*),

$$\begin{array}{c}
 \text{N} \\
 \parallel \\
 \text{N} = \text{C} - \text{NHC}_6\text{H}_5 \\
 | \quad \quad | \\
 \text{OC} \quad \quad \text{CH} \\
 | \quad \quad || \\
 \text{HN} - \text{CH}
 \end{array}$$

—The hydrochloride of this base was

obtained by boiling the above hydrochloride with strong hydrochloric acid. It formed colorless needles or prisms, from water or alcohol, which effervesced at 228° . This material was dissolved in hot water and ammonia was added, whereupon bunches of colorless needles separated. Unlike cytosine, this substance crystallizes without water of crystallization. It is fairly soluble in hot alcohol and, from this solvent, it separates in beautiful, colorless, six-sided plates. When slowly heated it melted at about 269° .

	Calculated for $C_{10}H_{10}ON_3$.	Found.
N	22.3	22.6

The *chlorplatinate* formed groups of radiating yellow prisms. A platinum and water determination agreed with the calculated for a normal salt with 1 molecule of water of crystallization. The formation of platinum chloride double salts with water of crystallization seems to be of frequent occurrence in the pyrimidine series.

	Calculated for $(C_{10}H_{10}ON_3)_2H_2PtCl_6 \cdot H_2O$.	Found.
Pt	24.24	24.31
H_2O	0.22	0.26

	$ \begin{array}{c} \text{N} = \text{C} - \text{NHC}_6\text{H}_5 \\ \quad \quad \\ \text{C}_6\text{H}_5\text{NHC} \quad \text{CH} \\ \quad \quad \\ \text{N} - \text{CH} \end{array} $	—The
--	---	------

2,6-Dianilinopyrimidine, C_6H_5NHC

hydrochloride of this base was obtained when 2-ethylmercapto-6-chlorpyrimidine was heated to 150° , with 2 molecular proportions of aniline. The compound formed arborescent needles from alcohol and melted at 197° .

	Calculated for $C_{16}H_{16}N_4Cl$.	Found.
N	18.76	18.59

The free base, obtained by boiling the hydrochloride with aqueous ammonia, crystallized from alcohol in six-sided plates. It is insoluble in water and fairly soluble in hot benzene and ether. It melted at 136° – 137° .

N	Calculated for $C_{10}H_{14}N_4$.	Found.
	21.38	21.42

	HN—CO	
2-Ethylmercapto-5-phenyluracil,	C_2H_5SC	CC_6H_5 , was ob-
	N—CH	

tained by condensing sodium phenylformylethylacetate¹ with the ethyl iodide addition-product of thiourea, in alkaline solution. The yield was very poor. The substance crystallized from alcohol in long, needle-like prisms, melting at 158° . In alcohol and hot water it is readily soluble.

N	Calculated for $C_{12}H_{12}ON_2S$.	Found.
	12.07	12.12

	HN—CO	
5-Phenyluracil,	OC	CC_6H_5 .—When the above compound
	HN—CH	

was digested on the steam-bath, with concentrated hydrochloric acid, for a number of hours, mercaptan was evolved and difficultly soluble material was obtained. The product was sparingly soluble in hot alcohol and water, but it separated from these solutions, on cooling, in a flocculent mass of what appeared to be microscopic plates. It did not melt at 350° . It is soluble in alkali and can be precipitated unaltered by hydrochloric acid.

N	Calculated for $C_{10}H_8O_2N_2$.	Found.
	14.89	14.87

The isomeric 4-phenyluracil has been described by Fischer and Roeder² and it was also obtained by one of us.³

NEW HAVEN, CONN.,
January, 1905.

¹ Wislicenus: Ber. d. chem. Ges., **20**, 2933 (1887).

² *Ibid.*, **34**, 3751 (1901).

³ Wheeler and Merriam: THIS JOURNAL, **29**, 490 (1903).

[Reprinted from the American Chemical Journal, Vol. XXXIV, No. 3.
September, 1905.]

Contributions from the Sheffield Laboratory of Yale University.

CXXV.—RESEARCHES ON PYRIMIDINES: THE ACTION OF AQUEOUS AND ALCOHOLIC AMMONIA AND ANILINE ON SOME HALOGEN AND MERCAPTO PYRIMIDINES.

[TENTH PAPER.]

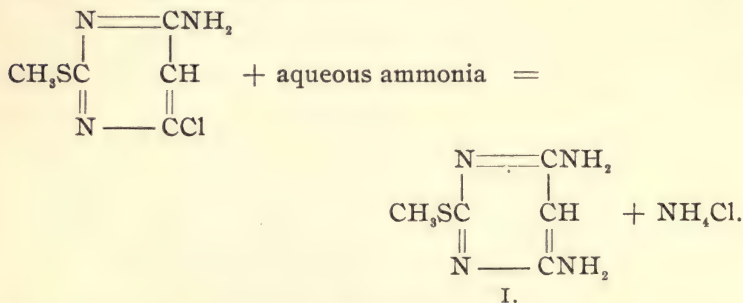
BY TREAT B. JOHNSON AND CARL O. JOHNS.

The object of this paper is to describe the behavior of certain halogen and mercapto pyrimidines towards ammoniacal solutions and aniline.

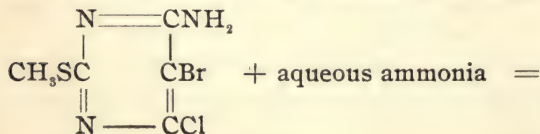
We have had occasion, in the preparation of aminopyrimidines, to use both aqueous and alcoholic solutions of ammonia to replace, with the amino group, halogens and mercapto radicals in pyrimidines. We have been greatly impressed, in the course of this work, with the remarkable difference in degree of reactivity of aqueous and alcoholic ammonia towards such pyrimidine derivatives.

In a recent publication from this laboratory, by Wheeler and

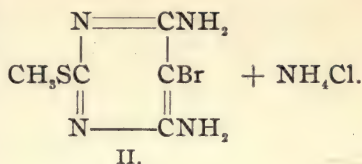
Jamieson,¹ it was shown that when 2-methylmercapto-5-methyl-4,6-dichlorpyrimidine was heated with alcoholic methylamine, only 1 chlorine atom was removed and 2-methylmercapto-4-chlor-5-methyl-6-methylamino pyrimidine was the product of the reaction. An analogous result was obtained when 2-methylmercapto-4,6-dichlorpyrimidine was heated with alcoholic ammonia. It was converted, practically quantitatively, into 2-methylmercapto-4-chlor-6-aminopyrimidine. They did not succeed in converting this chloraminopyrimidine into the corresponding diaminopyrimidine (I.) by heating with alcoholic ammonia. We now find that the 2-methylmercapto-4-chlor-6-aminopyrimidine is converted, quantitatively, into 2-methylmercapto-4,6-diaminopyrimidine (I.) when heated with aqueous ammonia, at 185°-195°:



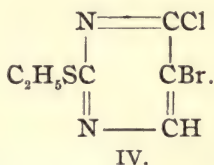
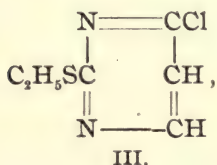
It seemed of interest, in connection with this result, to compare the behavior of aqueous and alcoholic ammonia towards 2-methylmercapto-4-chlor-5-brom-6-aminopyrimidine. This compound reacts in an analogous manner to the above 2-methylmercapto-4-chlor-6-aminopyrimidine. It can be recovered unaltered after heating with concentrated alcoholic ammonia, at 150°-160°. When heated with aqueous ammonia, under the same conditions, (150°-160°), it was converted, quantitatively, into 2-methylmercapto-5-brom-4,6-diaminopyrimidine,



¹ THIS JOURNAL, 32, 343 (1924).



It would appear, from the results of these two experiments, that a halogen is more easily replaced by the amino group when aqueous ammonia is used. In order to test this assumption further and to compare the action of ammoniacal solutions in another series, we have examined the comparative behavior of 2-ethylmercapto-6-chlorpyrimidine (III.) and 2-ethylmercapto-5-brom-6-chlorpyrimidine¹ (IV.) towards aqueous and alcoholic ammonia :



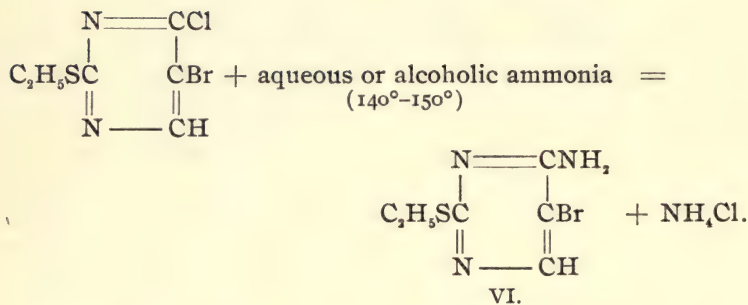
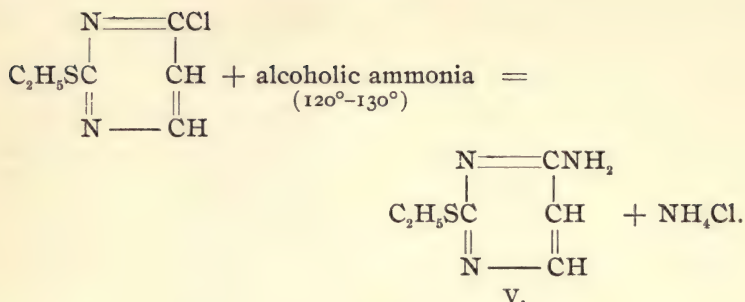
Wheeler and Johnson² observed that 2-ethylmercapto-6-chlorpyrimidine reacts with alcoholic ammonia, at 140°–150°, to form 2-ethylmercapto-6-aminopyrimidine³ (V.). We now find that this same chlorpyrimidine can be heated with aqueous ammonia, at the same temperature, (140°–150°) and be recovered unaltered. A most remarkable case of lack of analogy was observed when we examined the behavior of ammoniacal solutions towards 2-ethylmercapto-5-brom-6-chlorpyrimidine (IV.). This pyrimidine was converted, quantitatively, into 2-ethylmercapto-5-brom-6-aminopyrimidine (VI.) when heated with alcoholic ammonia, at 120°–130° and also when heated with aqueous ammonia, at 140°–150°.

¹ Wheeler and Johnson : THIS JOURNAL, 31, 603 (1904).

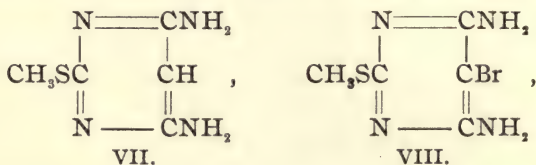
² *Ibid.*, 29, 492 (1903).

³ It has been our experience, since the publication of this paper, that the best yield of this 2-ethylmercapto-6-aminopyrimidine is obtained when the chloride is heated with alcoholic ammonia, at 120°–130°, for 3 or 4 hours.

T. B. J.



The abnormal behavior of ammoniacal solutions was also illustrated when we tried to replace the mercapto radical, in certain pyrimidines, with the amino group. 2-Methylmercapto-4,6-diaminopyrimidine¹ (VII.) and 2-methylmercapto-5-brom-4,6-diaminopyrimidine (VIII.) were recovered unaltered, after heating with both aqueous and alcoholic ammonia, at 205°-215°. These two negative results were of especial interest



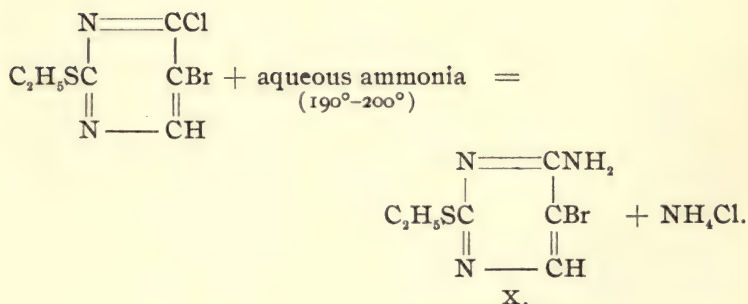
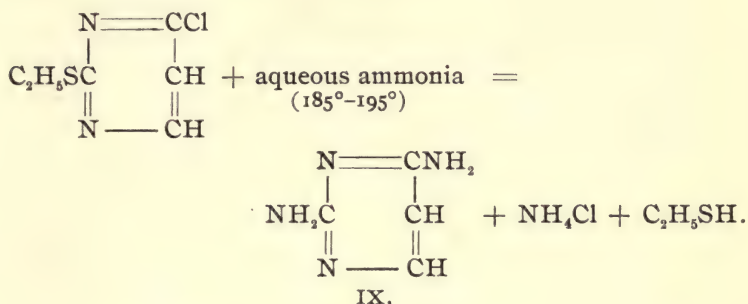
when compared with the behavior of 2-ethylmercapto-6-chlorpyrimidine² and 2-ethylmercapto-5-brom-6-chlorpyrimidine³ towards aqueous ammonia, at high temperatures. When

¹ Wheeler and Jamieson : *Loc. cit.*

² Wheeler and Johnson : *THIS JOURNAL*, **29**, 496 (1903).

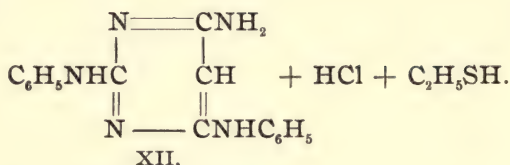
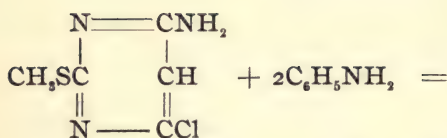
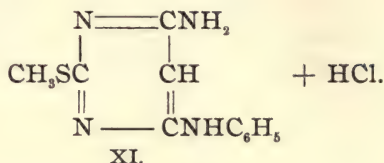
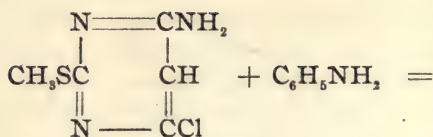
³ Wheeler and Johnson : *Ibid.*, **31**, 603 (1904).

2-ethylmercapto-6-chlorpyrimidine was heated with aqueous ammonia, at 185° – 195° , 2,6-diaminopyrimidine¹ (IX) was the product of the reaction. On the other hand, when 2-ethylmercapto-5-brom-6-chlorpyrimidine was heated, under practically the same conditions, (190° – 200°) with aqueous ammonia, the chlorine atom only was removed and 2-ethylmercapto-5-brom-6-aminopyrimidine (X.) was formed :

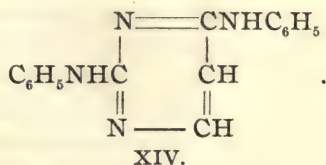
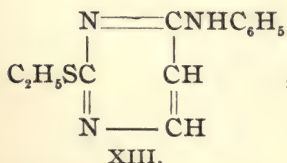


It has been our experience that a mercapto group is more easily replaced by the anilido— NHC_6H_5 —than by the amino group. When 2-methylmercapto-4-chlor-6-aminopyrimidine was heated with 1 molecular proportion of aniline, at 120° – 130° , 2-methylmercapto-4-anilido-6-aminopyrimidine (XI.) was formed. On the other hand, when heated with 2 molecular proportions of aniline, at 140° – 150° , 2,4-dianilido-6-aminopyrimidine (XII.) was the product of the reaction.

¹ Büttner : Ber. d. chem. Ges., **36**, 2233.



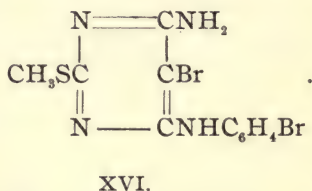
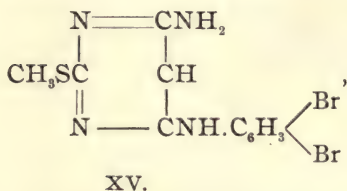
These results are analogous to that obtained by Wheeler and Bristol.¹ They observed that 2-ethylmercapto-6-chloropyrimidine reacted with 1 molecular proportion of aniline, at 100°, to form 2-ethylmercapto-6-anilidopyrimidine (XIII.). When the same mercaptochlorpyrimidine was heated with 2 molecular proportions of aniline, at 150°, it was converted into 2,6-dianilidopyrimidine (XIV.):



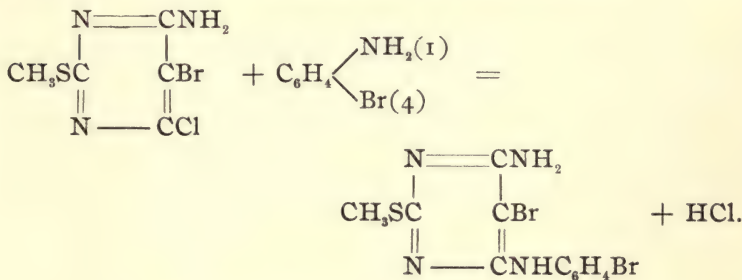
2-Methylmercapto-4-anilido-6-aminopyrimidine (XI.) reacts with bromine, in glacial acetic acid, to form a dibrom substituent.

¹ THIS JOURNAL, 33, 448 (1905).

tion-product, melting at 202° . In order to establish the structure of this body it was necessary to decide whether 1 or 2 bromine atoms had entered the benzene nucleus; whether 2-methylmercapto-4-dibromanilido-6-aminopyrimidine (XV.) or 2-methylmercapto-4-parabromanilido-5-brom-6-aminopyrimidine (XVI.) was the product of the reaction. The following experiment proved that formula XVI. represents the structure

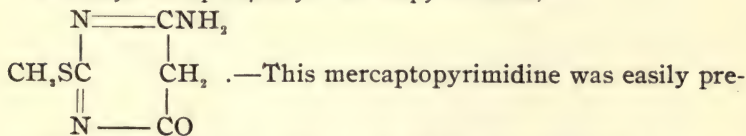


of this dibrompyrimidine. The same derivative, melting at 202° , was obtained when 2-methylmercapto-4-chlor-5-brom-6-aminopyrimidine was heated with parabromaniline :



EXPERIMENTAL.

2-Methylmercapto-4-oxy-6-aminopyrimidine,



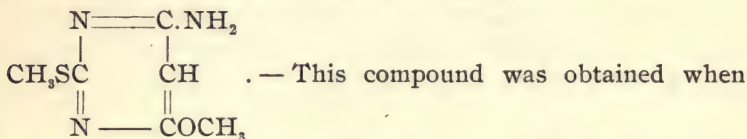
pared by dissolving 2-thio-4-oxy-6-aminopyrimidine¹ in alco-

¹ The 2-thio-4-oxy-6-aminopyrimidine used for this preparation was made according to Traube's directions, by condensing thiourea with cyanethylacetate, in presence of sodium ethylate. Ann. Chem. (Liebig), 331, 71.

hol, containing 1 molecular proportion of sodium ethylate and then warming on the steam-bath with 1 molecular proportion of methyl iodide. The reaction is exceedingly smooth and in a few minutes the mercapto derivative separates from the alcoholic solution. The pyrimidine was purified by evaporating the excess of alcohol and then washing the crystalline residue with cold water, to remove sodium iodide. It was difficultly soluble in hot alcohol, from which it separated in colorless plates. It decomposed at 267° with effervescence. The yield was practically quantitative. Analysis :

	Calculated for $C_5H_7ON_3S$.	Found.
N	26.75	26.97

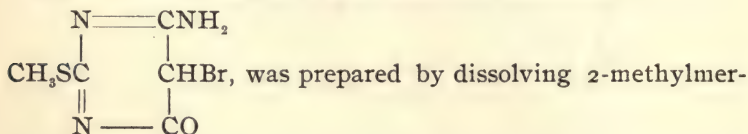
2-Methylmercapto-4-methoxy-6-aminopyrimidine,



2-thio-4-oxy-6-aminopyrimidine was warmed, in alcohol, with 2 molecular proportions of sodium ethylate and methyl iodide. It was soluble in acids but insoluble in alkali. It was purified by crystallizing from alcohol, from which it separated, on cooling, in long, well-developed prisms. It melted at 256° , without effervescence, to a clear oil. Analysis (Kjeldahl) :

	Calculated for $C_6H_9ON_3S$.	Found.
N	24.55	24.46

2-Methylmercapto-4-oxy-5-brom-6-aminopyrimidine,

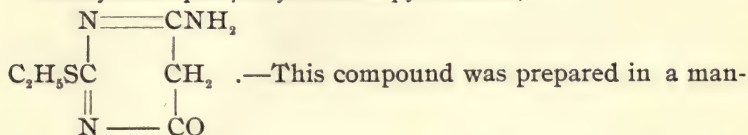


capto-4-oxy-6-aminopyrimidine in glacial acetic acid and then adding the calculated quantity of bromine. The bromine color disappeared at once and the pyrimidine separated as a beautiful, crystalline powder. It was difficultly soluble in water and

alcohol. It crystallized from hot acetic acid in slender prisms. It had no definite melting-point, but began to turn brown at 200° and did not melt below 300° . Analysis (Kjeldahl) :

	Calculated for $C_6H_6ON_3SBr$.	Found.
N	17.79	17.76

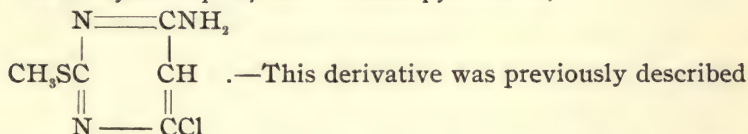
2-Ethylmercapto-4-oxy-6-aminopyrimidine,



ner similar to that used for the preparation of 2-methylmercapto-4-oxy-6-aminopyrimidine, by warming 2-thio-4-oxy-6-aminopyrimidine, in alcohol, with molecular proportions of sodium ethylate and ethyl bromide. It was very soluble in alcohol. It crystallized from water in long, slender prisms and melted at 216° – 217° , to a clear oil. Analysis (Kjeldahl) :

	Calculated for $C_6H_7ON_3S$.	Found.
N	24.56	24.37

2-Methylmercapto-4-chlor-6-aminopyrimidine,



by Wheeler and Jamieson,¹ who obtained it by heating 2-methylmercapto-4,6-dichlorpyrimidine with alcoholic ammonia. We find that it can be prepared more easily by treating 2-methylmercapto-4-oxy-6-aminopyrimidine with phosphorus oxychloride. The pyrimidine was boiled with an excess of phosphorus oxychloride until the evolution of hydrochloric acid ceased. The clear solution which resulted was then heated to 100° , under diminished pressure, to remove the excess of phosphorus oxychloride. A brittle, amorphous residue was obtained. This proved to be a mixture of the hydrochloride of the unaltered pyrimidine and an unstable phosphorus de-

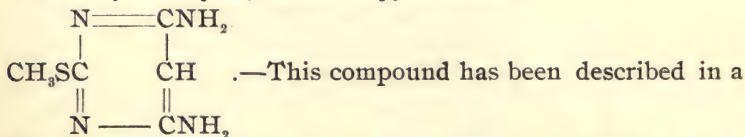
¹ THIS JOURNAL, 32, 343 (1904).

rivative of the mercaptochlorpyrimidine. The amorphous residue was carefully decomposed with ice-water. We obtained a clear, yellow solution, which was then made distinctly alkaline with ammonium hydroxide and concentrated by evaporation on the steam-bath. Upon cooling, a crystalline product separated which proved to be a mixture of the 2-methylmercapto-4-chlor-6-aminopyrimidine and unaltered 2-methylmercapto-4-oxy-6-aminopyrimidine. A separation of the two compounds was effected by washing with dilute sodium hydroxide solution, in which the chlorpyrimidine is insoluble. It was further purified by recrystallizing from water. It agreed in all its properties with the compound described by Wheeler and Jamieson,¹ except that we found it to melt at 132° instead of 126°-127°. Analysis (Kjeldahl) :

	Calculated for C ₆ H ₆ N ₃ SCl.	Found.
N	23.93	23.86

In our experiments in the preparation of the above 2-methylmercapto-4-chlor-6-aminopyrimidine we have usually obtained only about 45-50 per cent of the theoretical yield. In one experiment the yield corresponded to 59.6 per cent of the theoretical. In nearly every case we recovered, unaltered, about one-half of the 2-methylmercapto-4-oxy-6-aminopyrimidine. Phosphorus pentachloride was used in one experiment in place of phosphorus oxychloride, but the reaction was not as smooth and more decomposition-products were formed.

2-Methylmercapto-4,6-diaminopyrimidine,



previous paper from this laboratory.² We prepared it by heating the above 2-methylmercapto-4-chlor-6-aminopyrimidine with concentrated aqueous ammonia, at 185°-195°, for 5 hours. When the tube was opened we obtained a colorless solution which was immediately concentrated on the steam-

¹ *Loc. cit.*

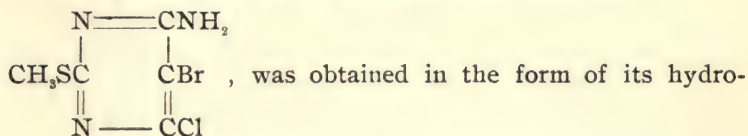
² Wheeler and Jamieson : *Loc. cit.*

bath. Upon cooling, a beautiful, crystalline body separated, which was purified by recrystallizing from water and alcohol. It deposited in lenticular-shaped crystals and melted at 184° – 185° , to a clear oil. Analysis (Kjeldahl) :

	Calculated for $C_5H_8N_4S$.	Found.
N	35.89	35.54

This mercaptodiaminopyrimidine is very stable in the presence of aqueous and alcoholic ammonia solutions. It was recovered, unaltered, after heating with concentrated aqueous ammonia, for 7 hours, at 205° – 215° . It was then heated with a saturated, alcoholic solution of ammonia, for 7 hours, at 205° – 215° . The pyrimidine was again recovered unaltered and melted sharply at 184° – 185° .

2-Methylmercapto-4-chlor-5-brom-6-aminopyrimidine,



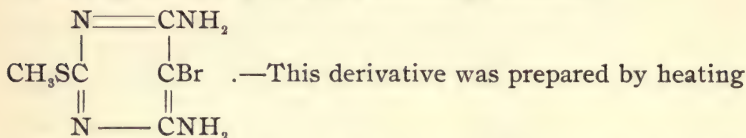
bromic acid salt, when a molecular proportion of bromine was added to an acetic acid solution of 2-methylmercapto-4-chlor-6-aminopyrimidine. The hydrobromide sintered at about 180° – 190° and then decomposed at 208° , with violent effervescence. It was purified for analysis by crystallizing from acetic acid, from which it separated, on cooling, in stout prisms. Analysis :

	Calculated for $C_5H_6N_4SClBr_2$.	Found.
N	12.51	12.56

The pyrimidine base was easily obtained from its salt by treating with a 10 per cent solution of sodium hydroxide. It was difficultly soluble in water and melted at 165° , without effervescence. The pyrimidine showed a strong tendency to occlude water. In order to thoroughly dry it for analysis it was necessary to heat for about 1 hour, at 115° – 120° . Analysis :

	Calculated for $C_6H_5N_3SClBr$.	Found.
N	16.50	16.38

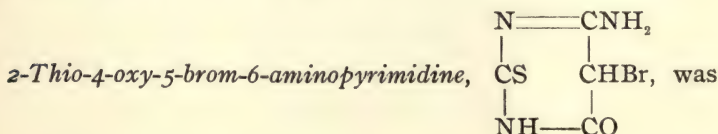
2-Methylmercapto-5-brom-4,6-diaminopyrimidine,



2-methylmercapto-4-chlor-5-brom-6-aminopyrimidine with aqueous ammonia, for 4 hours, at 150° – 160° . When the tube was opened the compound had separated in magnificent prisms. Some of these crystals measured 3 cm. in length. The pyrimidine crystallized from hot water in beautiful prisms and melted at 192° , to a clear oil. The yield corresponded to about 80 per cent of the theoretical. Analysis (Kjeldahl) :

	Calculated for $C_6H_7N_4SBr$.	Found.
N	23.83	23.77

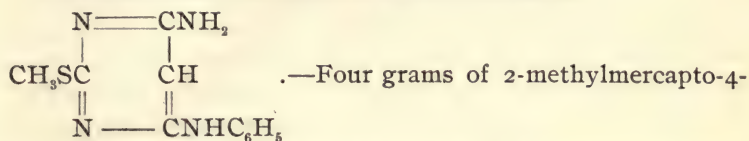
An attempt was made to prepare this diaminopyrimidine by heating the 2-methylmercapto-4-chlor-5-brom-6-aminopyrimidine with alcoholic ammonia. After heating for 4 hours, at 150° – 160° , it was recovered unaltered. The alcohol solution gave only a faint test for chlorine. The 2-methylmercapto-5-brom-4,6-diaminopyrimidine is very stable in contact with aqueous and alcoholic ammonia, at higher temperatures. After heating for 8 hours, at 180° – 190° , with concentrated, aqueous ammonia, it was recovered unaltered. It was again heated with fresh aqueous ammonia, for 5 hours, at 200° – 210° . Only a trace of mercaptan could be detected and the pyrimidine was recovered, melting sharply at 192° . A similar result was obtained when it was heated with concentrated, alcoholic ammonia, for 4 hours, at 200° – 214° .



made by adding a molecular proportion of bromine to an acetic acid solution of 2-thio-4-oxy-6-aminopyrimidine. It separated from the acetic acid in granular crystals. It was difficultly soluble in acetic acid and insoluble in water. It did not melt below 300°. Analysis (Kjeldahl) :

	Calculated for $C_4H_4ON_8SBr$.	Found.
N	18.91	18.68

2-Methylmercapto-4-anilido-6-aminopyrimidine,



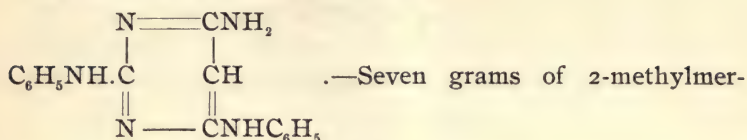
chlor-6-aminopyrimidine were heated with 1 molecular proportion of aniline, for 6 hours, at 100°–130°. A clear, red varnish was obtained, which dissolved in boiling alcohol. Upon cooling, rhombic-shaped prisms separated. They were purified by recrystallizing from alcohol and melted at 121°, with violent effervescence. A nitrogen determination agreed with the calculated for a dihydrochloride :

$$\begin{array}{c}
 \text{N}=\text{CNH}_2 \\
 | \qquad | \\
 \text{CH}_3\text{SC} \quad \text{CH} \\
 || \qquad || \\
 \text{N}=\text{CNHC}_6\text{H}_5
 \end{array}
 \quad .2\text{HCl.}$$

	Calculated for $C_{11}H_{14}N_4SCl_2$.	I.	Found.	II.
N	18.36	18.01		18.11

The free pyrimidine base was obtained by triturating the hydrochloric acid salt with an excess of dilute sodium hydroxide. The base crystallized from benzene in clusters of microscopic prisms and melted at 124°, without effervescence, to a clear oil. It gave a strong test for sulphur, but contained no chlorine. Analysis (Kjeldahl) :

	Calculated for $C_{11}H_{12}N_4S$.	Found.
N	24.13	23.82

2,4-Dianilido-6-aminopyrimidine,

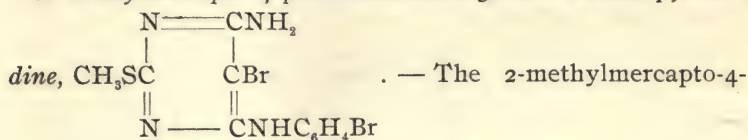
capto-4-chlor-6-aminopyrimidine were heated with 2 molecular proportions of aniline, at $140^\circ\text{--}150^\circ$, for 10 hours. A slow effervescence took place and methylmercaptan was constantly given off. Upon cooling, the reaction-product hardened to an amorphous solid. This was treated with a warm solution of sodium hydroxide, when it melted to a heavy, thick oil. The excess of aniline was then removed by distillation with steam. On cooling, a crystalline cake remained, which weighed 10 grams. This pyrimidine was very difficult to purify. It was extremely soluble in cold alcohol, benzene and ether. It dissolved in hot water, but separated, on cooling, as an oil which finally solidified to a hard, amorphous mass. To effect purification it was converted into its sulphuric acid salt. This salt is insoluble in cold water. When warmed with water it dissociates into the free base and sulphuric acid. It can be crystallized from alcohol containing free sulphuric acid. It separated from alcohol in granular crystals and melted at $190^\circ\text{--}193^\circ$, with effervescence. Analysis (Kjeldahl) :

	Calculated for $\text{C}_{10}\text{H}_{15}\text{N}_5 \cdot \text{H}_2\text{SO}_4$.	Found.
N	18.66	18.73

The pyrimidine base was obtained from this sulphuric acid salt by warming with a dilute solution of ammonium hydroxide. It separated as an oil, which finally solidified on standing. After drying over sulphuric acid for 24 hours, it melted at $65^\circ\text{--}70^\circ$, to a slightly turbid oil. It is extremely soluble in the ordinary organic solvents. Analysis (Kjeldahl) :

	Calculated for $\text{C}_{10}\text{H}_{15}\text{N}_5$.	Found.
N	25.27	24.81

2-Methylmercapto-4-parabromanilido-5-brom-6-aminopyrimidine



anilido-6-aminopyrimidine was dissolved in glacial acetic acid and bromine carefully added, as long as the bromine color disappeared. Stout prisms separated immediately, which were difficultly soluble in acetic acid. They decompose, with violent effervescence, at about 290° , turning somewhat brown at 210° – 220° . A nitrogen determination agreed with the calculated for the hydrobromic acid salt of a dibrom-substitution-product :

	Calculated for $\text{C}_{11}\text{H}_{11}\text{N}_4\text{SBr}_3$.	Found.
N	11.89	12.29

The pyrimidine base was obtained by treating the hydrobromic acid salt with a 10 per cent solution of sodium hydroxide. It melted at 202° , without effervescence, to a clear oil. A nitrogen determination agreed with the calculated for 2-methylmercapto-4-bromanilido-5-brom-6-aminopyrimidine :

	Calculated for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{SBr}_2$.	Found.
N	14.36	14.80

In order to establish the structure of this dibrompyrimidine derivative we have prepared it in the following manner : 3.6 grams of 2-methylmercapto-4-chlor-5-brom-6-aminopyrimidine were heated with 2.4 grams of parabromaniline, for 4 hours, at 120° – 130° . A violet-colored oil was obtained which solidified on cooling. The material was insoluble in water, but soluble in hot acetic acid. In order to obtain the free base the substance was triturated with sodium hydroxide, filtered and then boiled in acetic acid, with animal charcoal, to remove the color. On cooling, long, slender prisms were obtained, which melted, without effervescence, at 202° . When some of this base was mixed with the above product, obtained by brominating 2-methylmercapto-4-anilido-6-aminopyrimidine (m. p.

202°), the melting-point was not lowered. Analysis (Kjeldahl) :

	Calculated for $C_{11}H_{10}N_4SBr_2$.	Found.
N	14.36	14.31
$ \begin{array}{c} \text{N}=\text{CNH}_2 \\ \qquad \\ \text{CO} \qquad \text{CBr} \\ \qquad \\ \text{NH}-\text{CCl} \end{array} $		
<i>2-Oxy-4-chlor-5-brom-6-aminopyrimidine,</i>		

This compound was obtained, in the form of its hydrobromic acid salt, when 2-oxy-4-chlor-6-aminopyrimidine was suspended in glacial acetic acid and treated with 1 molecular proportion of bromine. The hydrobromide separated as an orange-colored powder, which decomposed at 230°–240°, with effervescence. In order to obtain the free base the crude salt was warmed with a solution of dilute sodium hydroxide. When the alkali solution was acidified with dilute acetic acid the base separated as a crystalline precipitate. It crystallized from hot water in clusters of microscopic prisms and showed no definite melting-point, but began to turn brown at 210° and decomposed at about 230°, with violent effervescence. Analysis :

	Calculated for $C_4H_3ON_3ClBr$.	Found.
N	18.70	18.68

Action of Aqueous Ammonia on 2-Ethylmercapto-6-chlorpyrimidine.

At 140°–150°.—After heating with aqueous ammonia, for 4 hours, at 140°–150°, the pyrimidine was recovered unaltered.

At 185°–195°.—The chlorpyrimidine was heated with aqueous ammonia, for 3 hours, at 185°–195°. The ammoniacal solution was then evaporated to dryness. The crystalline residue was warmed with alcohol and filtered from the undissolved ammonium chloride. The alcoholic filtrate was then evaporated to dryness and the residue again dissolved in water. The chlorine was removed by precipitating with silver sulphate, then the sulphuric acid removed with barium hy-

droxide and the excess of barium with carbon dioxide. When the solution was evaporated to dryness we obtained a crystalline base which had all the properties of 2,6-diaminopyrimidine. It was extremely soluble in water. The base was identified by means of its platinum chloride salt. Analysis:

	Calculated for (C ₄ H ₅ N ₄) ₂ .H ₂ PtCl ₆ .	Found.
Pt (194.8)	30.9	30.5

*Action of Aqueous Ammonia on 2-Ethylmercapto-5-brom-6-chlor-pyrimidine.*¹

At 140°-150°.—When the pyrimidine was heated with aqueous ammonia, at 140°-150°, for 4 hours, it was converted, quantitatively, into 2-ethylmercapto-5-brom-6-aminopyrimidine, melting sharply at 124°-125°.

At 185°-195°.—After heating for 4 hours, at 160°-170° and then for 3 hours, at 185°-195°, the 2-ethylmercapto-5-brom-6-aminopyrimidine was again obtained, melting at 124°-125°.

NEW HAVEN, CONN.,
May 1, 1905.

¹ Wheeler and Johnson: *Loc. cit.*



Printed from the American Chemical Journal, Vol. XXXIV. No. 3.
September, 1904.

Contributions from the Sheffield Laboratory of Yale University.

CXXVI.—RESEARCHES ON PYRIMIDINES: 2-ETHYL-
MERCAPTO-5-AMINO-6-OXYPYRIMIDINE.

[ELEVENTH PAPER.]

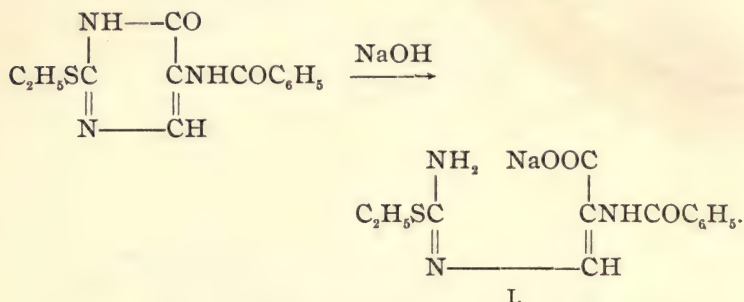
BY TREAT B. JOHNSON.

The work described in this paper was undertaken with the object of investigating the formation and properties of 2-ethyl-mercapto-5-amino-6-oxypyrimidine. The examination of this pyrimidine was of particular interest in the study of oxy-diaminopyrimidines, because it offered the possibility of synthesizing both 2,5-diamino-6-oxypyrimidine and 2-oxy-5,6-diaminopyrimidine. The preparation of 2,5-diamino-6-oxypyrimidine from this mercaptopyrimidine will be discussed in a later paper.

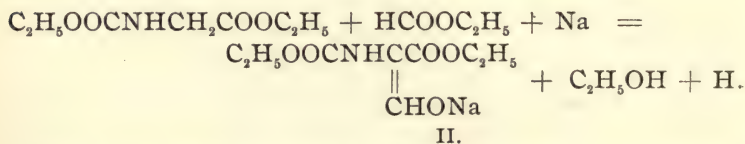
In a previous paper² from this laboratory, it was shown that

² Johnson and Clapp: *THIS JOURNAL*, **32**, 131 (1904).

ethyl formate condenses, in benzene, with ethyl hippurate, in the presence of metallic sodium, to form the sodium salt of formylethylhippurate.¹ This salt condensed very readily with pseudoethylthiourea to give the benzoyl derivative of 2-ethyl-mercapto-5-amino-6-oxypyrimidine. Attempts to hydrolyze this acyl derivative to the free pyrimidine, (V.), were unsuccessful. Acids could not be used for the hydrolysis on account of the ease with which the mercapto radical was displaced by hydroxyl. When boiled with sodium hydroxide the pyrimidine ring was opened, to form a sodium salt of α -benzoylamino- β -pseudoethylthioureaacrylic acid (I.). This acid was unstable and immediately condensed again to the pyrimidine, when the sodium salt was treated with acids :



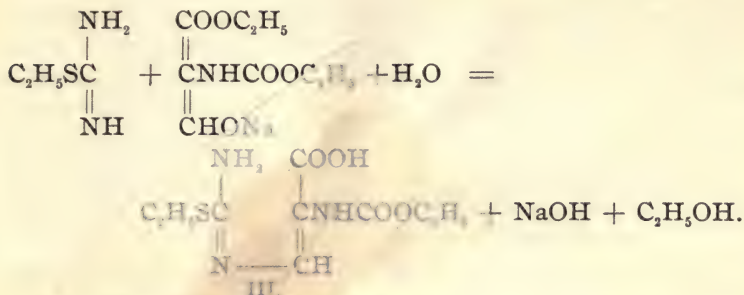
I now find that ethyl formate condenses very smoothly, in benzene, with carbethoxyaminoethylacetate, in the presence of metallic sodium, to form the sodium salt of formylcarbethoxyaminoethylacetate (II.) :



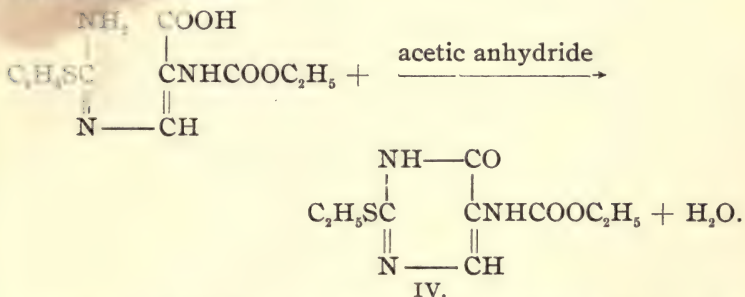
This sodium salt condensed at the ordinary temperature; in aqueous solution, with pseudoethylthiourea, giving α -carbethoxyamino- β -pseudoethylthioureaacrylic acid (III.). The yield

¹ Erlenmeyer, in his recent paper on the synthesis of serin and cystine, has shown that this salt can be obtained very smoothly by condensing ethyl formate with ethyl hippurate, in alcohol, by means of sodium ethylate. *Ann. Chem. (Liebig)*, **337**, 251.

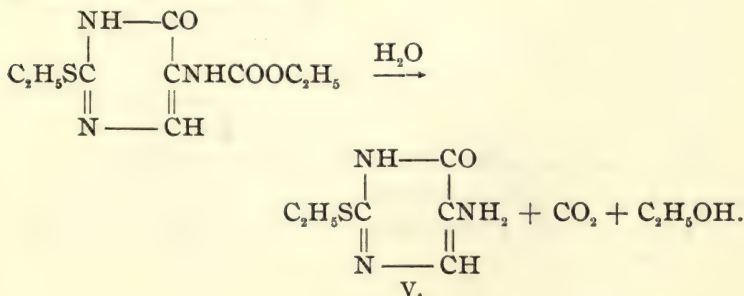
of this acid corresponded to about 40–50 per cent of the theoretical :



In no case have I succeeded in isolating the pyrimidine—2-ethylmercaptio-5-carbethoxyamino-6-oxypyrimidine, (IV.)—as a product of this condensation. This compound, nevertheless, was easily obtained when the acrylic acid was warmed with acetic anhydride.



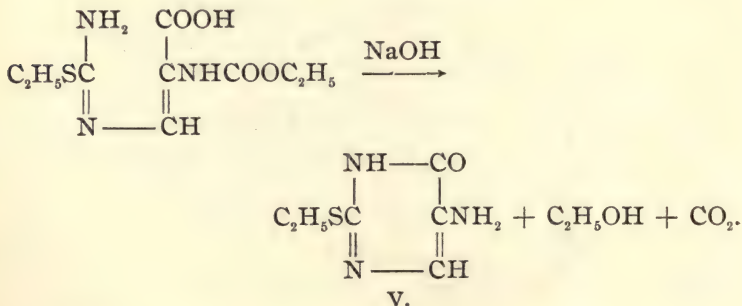
When this pyrimidine, (IV.) was boiled with a solution of sodium hydroxide, it was converted into 2-ethylmercapto-5-amino-6-oxypyrimidine, (V.) :



The formation of the above acrylic acid, (III.) is of interest as the second case in which the formation of intermediate products has been observed in the preparation of pyrimidines from pseudothiureas. The first case observed was described by Johnson and Clapp,¹ in a paper on the preparation of 2-amino-5-methyl-6-oxypyrimidine from guanidine and the sodium salt of formylethylpropionate. They not only observed the formation of an intermediate acrylic acid in this condensation, but also were able to show that it was capable of existing in two stereoisomeric modifications.

The α -carbethoxyamino- β -pseudoethylthiourea acrylic acid (III.) is especially characterized by its stability towards cold alkali solutions. On account of this pronounced stability I have designated it as the *trans*-modification. Under the experimental conditions I used I did not succeed in isolating an unstable *cis*-modification.

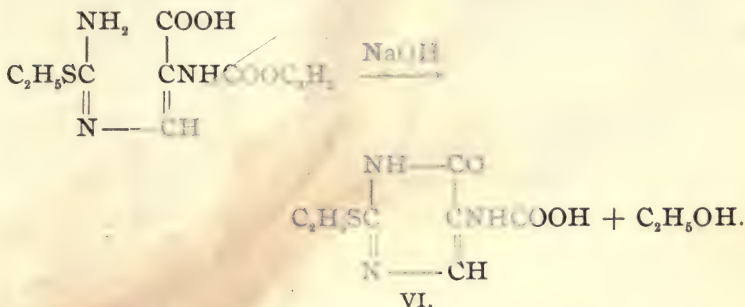
The *trans*-acid is very easily decomposed when boiled with strong and dilute solutions of sodium hydroxide. When it was boiled for a few minutes, with a strong sodium hydroxide solution and the solution then neutralized with acids or carbon dioxide, it was converted, almost quantitatively, into 2-ethylmercapto-5-amino-6-oxypyrimidine (V.) :



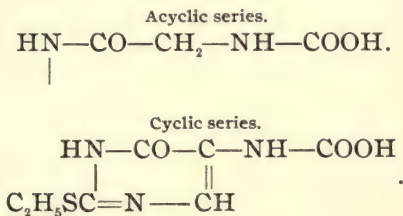
This interesting saponification and condensation of the *trans*-acid to the mercaptoaminopyrimidine, (V.) led me to examine its behavior when warmed with a dilute solution of sodium

¹ *Loc. cit.*

hydroxide. The experimental data at hand seem to indicate that the *trans*-acid is saponified by dilute alkali to an intermediate 2-ethylmercapto-5-carboxylamino-6-oxy-pyrimidine, (VI.).



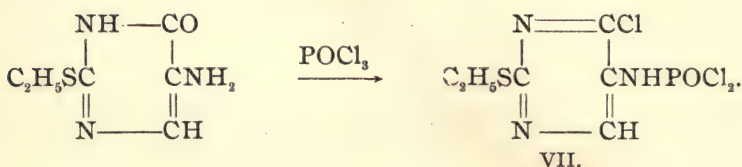
The existence of this intermediate carbamic acid is particularly interesting because of the fact that it contains a cyclic polypeptide linking. Analogous acids in the acyclic series have been obtained by Fisher,¹ in his important researches on polypeptides. The relationship between the above pyrimidine, (VI.) and a true polypeptide linking is made evident by the following comparison :



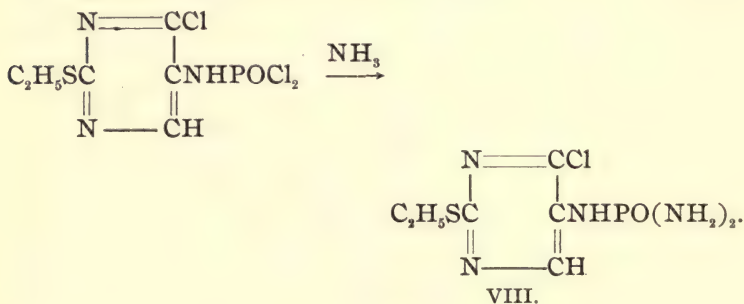
It has been the usual experience, during the investigation of pyrimidines in this laboratory, to find that a mercaptooxy-pyrimidine reacts normally with phosphorus oxychloride, or phosphorus pentachloride, to give a chlorpyrimidine derivative. It has also been observed repeatedly that the resulting chlorpyrimidines are obtained combined with phosphorus oxychloride. These phosphorus compounds are very unstable and

¹ Ber. d. chem. Ges., 36, 2094 (1903).

are decomposed by water, with formation of the free chlorpyrimidine. I now find that 2-ethylmercapto-5-amino-6-oxy-pyrimidine reacts with phosphorus oxychloride to form a phosphorus compound which is abnormally stable. The analytical determinations agree with the calculated for a phosphoryldichloride derivative (VII.) :



This phosphorus derivative could be warmed with water without decomposition. When it was heated with alcoholic ammonia 2 chlorine atoms were removed and a stable compound was obtained, which I have, provisionally, represented as a phosphoryltriarnide derivative,¹ (VIII.) :

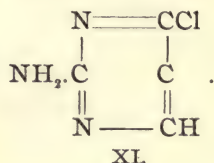
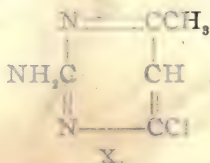
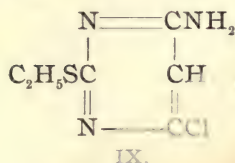


The fact that this amino radical should show such pronounced affinity for phosphorus, is of interest. In a recent communication from this laboratory² it has been shown that the isomeric 2-ethylmercapto-4-oxy-6-aminopyrimidine reacts perfectly normally with phosphorus oxychloride, to form 2-ethylmercapto-4-chlor-6-aminopyrimidine, (IX.). Furthermore, Gabriel and

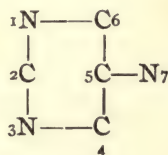
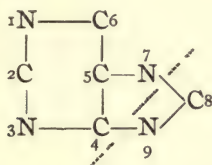
¹ These phosphoryl pyrimidine derivatives will receive further attention in this laboratory.

² Johnson and Johns: Preceding paper.

Colman¹ have shown that 2-amino-4-oxy-6-methylpyrimidine is converted, by phosphorus oxychloride, into 2-amino-4-chlor-6-methylpyrimidine. Later,² they observed that 2-amino-6-oxypyrimidine (isocytosine) also reacts normally with phosphorus oxychloride, to give 2-amino-6-chlorpyrimidine, (XI.).



In a previous publication on "Die Nucleinsäure des Weissenembryos," Osborne and Harris³ have produced evidence to show that, in triticonucleic acid, there is a direct union between phosphorus and the nitrogen of the purine bases. Gurian,⁴ in a recent publication, has produced more evidence that supports the fact of this union in the nucleic acid molecule. Furthermore, his experiments tend to show that it is the nitrogen atom occupying position 7 in the purine molecule that is probably joined to the phosphorus. It is of interest to note, in this connection, that the nitrogen atom in the aminopyrimidine, (V.) which shows such affinity for phosphorus, corresponds to the nitrogen atom occupying position 7 in the purine molecule.



EXPERIMENTAL.

Sodium Salt of Formylcarbethoxyaminoethylacetate,
 $\text{C}_2\text{H}_5\text{OOCNHC} : (\text{CHONa})\text{COOC}_2\text{H}_5$.—The carbethoxyaminoethylacetate, used for the preparation of this sodium salt, was

¹ Ber. d. chem. Ges., **32**, 2921.

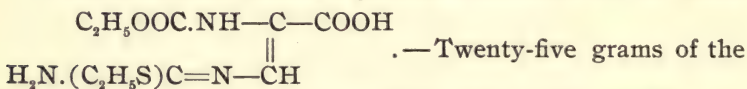
² *Ibid.*, **36**, 3383.

³ Z. physiol. Chem., **36**, 85 (1902).

⁴ Ber. d. chem. Ges., **37**, 708.

prepared by Fisher's¹ method, from the hydrochloride of aminoethylacetate and chlorethylformate. The hydrochloride of aminoethylacetate was prepared according to Klages'² directions, from methyleneaminoacetonitrile. The method is extremely suitable for preparing large quantities of this hydrochloride. Ethyl formate condenses very smoothly with carbethoxyaminoethylacetate, in the presence of sodium, in either benzene or ether; but it has been my experience that the condensation is much smoother and more rapid when benzene is used as the diluent. This sodium salt is much more stable in contact with the air than the sodium salt of formylethylacetate. I also found that the condensation could safely be accelerated by gently warming the benzene solution on the steam-bath. The purity of the salt obtained was not affected by this treatment. In all my condensations the yield of crude sodium salt has been about equal to the weight of carbethoxyaminoethylacetate used.

Trans-α-carbethoxyamino-β-pseudoethylthiourea Acrylic Acid.



sodium salt of formylcarbethoxyaminoethylacetate were dissolved in water and added to an aqueous solution of pseudoethylthiourea, which was previously prepared by treating 17 grams of pseudoethylthiourea hydrobromide with 6 grams of potassium hydroxide. The clear solution, which resulted, was then allowed to stand for a few hours, at the ordinary temperature. Upon neutralizing with acetic acid a beautiful, white, crystalline compound separated. It was insoluble in alcohol and cold water. It could be dissolved, repeatedly, in cold solutions of sodium hydroxide and be precipitated, unaltered, by acids. It was purified for analysis by recrystallizing from hot water. It separated as a colorless powder, consisting of microscopic prisms. It showed no sharp melting-point but decomposed, with effervescence, at 259°. A yield of 11.5 grams of crude material was obtained. For analysis it was dried at 100°.

¹ Ber. d. chem. Ges., 36, 2107.

² *Ibid.*, 36, 1508.

0.1574 gram substance gave 0.1341 gram BaSO_4 (Carius).

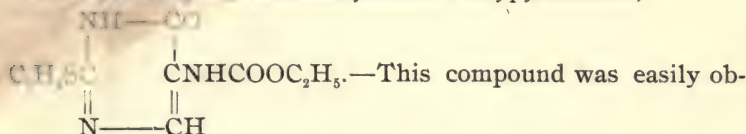
	Calculated for $\text{C}_9\text{H}_{16}\text{O}_4\text{N}_3\text{S}$.	Found.
N	16.00	15.75
S	12.25	11.70

The following table is given to show the comparative yields obtained in four different preparations of this *trans*-acid :

Table.

Weight of carbethoxyaminoethyl acetate used. Grams.	Weight of sodium salt of condensation-product Grams.	Weight of <i>trans</i> -acid. Grams.	Percentage of theoretical. Per cent.
30	32	11.0	40
20	25	11.5	46
40	45	20.0	45
40	45	19.5	44

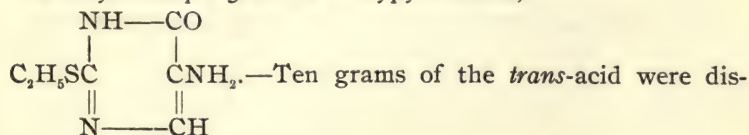
2-Ethylmercapto-5-carbethoxyamino-6-oxypyrimidine,



tained when the *trans*-acid, above described, was dissolved in warm acetic anhydride. On adding water the pyrimidine separated in prisms. It was easily purified by recrystallizing from 15 per cent acetic acid and separated, on cooling, in well-developed prisms, which melted, without effervescence, at 189° – 190° , to a clear oil. The pyrimidine dissolves in sodium hydroxide solution and is reprecipitated, unaltered, by acids. It was also obtained, in an impure condition, when the *trans*-acid was boiled with glacial acetic acid. Analysis :

	Calculated for $\text{C}_9\text{H}_{13}\text{O}_3\text{N}_3\text{S}$.	Found.
N	17.28	17.35

2-Ethylmercapto-5-amino-6-oxypyrimidine,

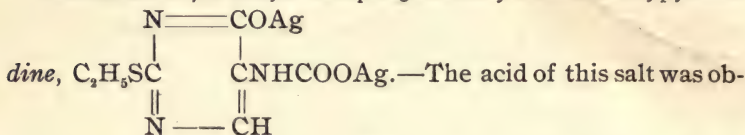


solved in 50 cc. of water, containing 5 grams of sodium hydrox-

ide. The alkaline solution was boiled for about 20 minutes and then allowed to stand for 30 minutes. When the alkaline solution was made slightly acid with acetic acid the pyrimidine separated in beautiful, needle-like crystals, which melted, to a clear oil, at about 155° . It was purified by recrystallizing from hot water. It separated in clusters of radiating needles and, without effervescence, melted at 160° , to a clear oil. The yield was practically quantitative. This pyrimidine was also formed when 2-ethylmercapto-5-carbethoxyamino-6-oxypyrimidine was boiled with sodium hydroxide. Analysis (Kjeldahl) :

	Calculated for $C_6H_9ON_3S$.	Found.
N	24.56	24.34

Disilver Salt of 2-Ethylmercapto-5-carboxylamino-6-oxypyrimi-

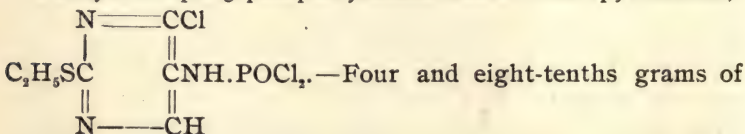


tained, in solution, from two different preparations of the *trans*-acid. It was formed by boiling the latter with a dilute solution of sodium hydroxide. It was very soluble in water and was not precipitated from the alkali solution by mineral acids or carbon dioxide. The disilver salt was obtained, after acidifying the alkaline solution with nitric acid, by adding a slight excess of 20 per cent silver nitrate solution. The salt was difficultly soluble in water and showed no crystalline form. Analysis of the substance, thoroughly dried over sulphuric acid :

0.1399 gram silver salt gave 0.0707 gram metallic silver.

	Calculated for $C_7H_7O_3N_3S_2Ag_2$.	Found.
Ag	50.35	50.53

2-Ethylmercapto-5-phosphoryldichloramino-6-chloropyrimidine,



2-ethylmercapto-5-amino-6-oxypyrimidine were warmed, on a sand-bath, with an excess of phosphorus oxychloride. A reaction set in at once, with evolution of hydrochloric acid gas. After this ceased the excess of phosphorus oxychloride was removed by distillation under diminished pressure. I obtained a yellow, amorphous residue. When this was treated with water very little heat was evolved and a yellow, crystalline deposit remained suspended in the water. This residue was filtered and then warmed with water on the steam-bath, to destroy any phosphorus oxychloride. A thick, oily product, insoluble in water, was obtained by this treatment; it immediately solidified, on cooling, to a hard, crystalline cake. It was insoluble in the ordinary organic solvents and also in ammonium hydroxide. When treated with a solution of sodium hydroxide it showed a very peculiar behavior. The product was insoluble in sodium hydroxide, but gradually underwent decomposition and the solution assumed a dark green color. It gave strong tests for sulphur and phosphorus. It had no sharp melting-point, but decomposed at about 247° – 250° . Analysis :

	Calculated for $C_6H_7ON_3SCl_3P$.	Found.
N	13.70	13.41

2-Ethylmercapto-5-phosphoryltri-amino-6-chlorpyrimidine,

$$\begin{array}{c}
 \text{N}=\text{CCl} \\
 | \qquad \qquad | \\
 \text{C}_2\text{H}_5\text{SC} \quad \quad \text{CNHPO} \begin{cases} \text{NH}_2 \\ \text{NH}_2 \end{cases} \\
 || \qquad \qquad || \\
 \text{N} \text{---} \text{CH}
 \end{array}$$

—This complicated derivative

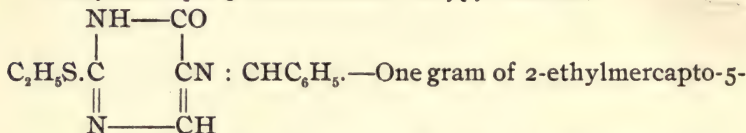
was obtained when the above chloride was heated with alcoholic ammonia, for 3 hours, at 160° – 165° . When the tube was opened there was no pressure and only a slight odor of mercaptan was noticeable. The pyrimidine was suspended in the alcohol and had a green, metallic appearance. It was insoluble in water and the ordinary organic solvents. It gave strong tests for chlorine, sulphur and phosphorus. It had no characteristic melting-point, but began to sinter at about 258° and decomposed 290° – 300° , according to the rate of heating. Analysis :

	Calculated for $C_6H_{11}ON_5SCIP.$	Found.
N	26.16	26.12

Sodium Salt of α -Benzoylamino- β -pseudoethylthiourea Acrylic Acid, $H_2N(C_2H_5S)C : NCH : C(NHCOC_6H_5)COONa$.—This salt was obtained when 2-ethylmercapto-5-benzoylamino-6-oxypyrimidine¹ was boiled with a solution of sodium hydroxide. The sodium salt separated, on cooling, in needles. It crystallized from alcohol in needles and melted, with effervescence, at 124° – 125° . When treated with acids it was converted into the unaltered pyrimidine, melting at 239° . Analysis :

	Calculated for $C_{13}H_{14}O_3N_3S.Na.H_2O.$	Found.
N	12.61	12.45

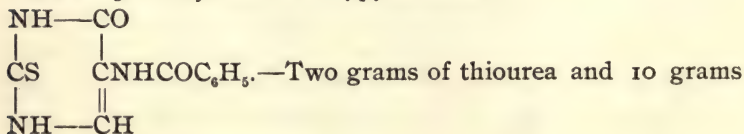
2-Ethylmercapto-5-benzalamino-6-oxypyrimidine,



amino-6-oxypyrimidine was warmed with 1 molecular proportion of benzaldehyde, for 1–2 hours, at 160° – 180° . Water was given off immediately on warming and the material solidified to a crust in the hot bath. The pyrimidine crystallized from alcohol as a microscopic powder, from benzene in beautiful, rhombic plates or flattened prisms, melting at 185° – 187° , to a clear oil. By prolonged boiling with water or dilute alcohol it was slowly decomposed into benzaldehyde and the unaltered pyrimidine. Analysis :

	Calculated for $C_{13}H_{13}ON_3S.$	Found.
N	16.21	16.00

2-Thio-5-benzoylamino-6-oxypyrimidine,

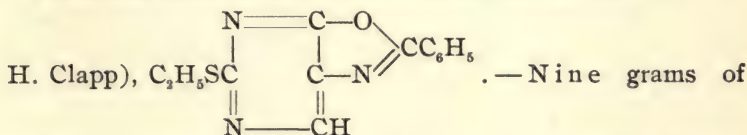


¹ Johnson and Clapp : *Loc. cit.*

of the sodium salt of formylethylhippurate¹ were dissolved in 50 cc. of water and warmed, on the steam-bath, for about 20 minutes. The solution assumed, at once, a turbid appearance, due to the separation of ethylhippurate. Upon cooling, a small amount of crystalline material separated from the alkaline liquid. This was removed by filtration and dried on the oven. No further precipitate was obtained when the alkaline solution was acidified with acetic acid. The crystalline product was purified by crystallizing from acetic acid. It separated in plates and decomposed at 300°-310°, according to the rate of heating. It was soluble in sodium hydroxide and was reprecipitated, unaltered, by acids. It was insoluble in water and alcohol. When it was boiled with hydrochloric acid it was decomposed with evolution of hydrogen sulphide. Analysis (Kjeldahl):

	Calculated for C ₁₁ H ₉ O ₂ N ₂ S.	Found.
N	17.00	16.86

2-Ethylmercapto-5,6-(μ-phenyloxazoline)pyrimidine (By S.



2-ethylmercapto-5-benzoylamino-6-oxypyrimidine¹ were heated to boiling with 50 cc. of phosphorus oxychloride, for 3 hours. Hydrochloric acid was evolved continuously. The excess of phosphorus oxychloride was then distilled off under diminished pressure. I obtained a thick varnish, which would not solidify. This was treated with cold water, to destroy any excess of phosphorus oxychloride. Heat was evolved and a white, crystalline solid separated. This was thoroughly washed with water and purified by recrystallizing from alcohol. It melted, without effervescence, at 108°-109° to a clear oil. It was free from chlorine. Analysis (Carius):

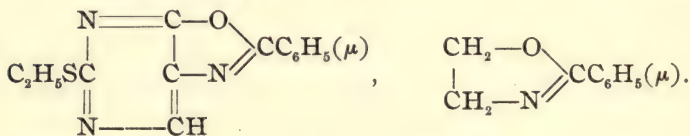
0.1399 gram substance gave 0.1268 gram BaSO₄.

¹ Johnson and Clapp: *Loc. cit.*

S	Calculated for $C_{13}H_{11}N_3OS.$	Found.
	12.45	12.43

The compound was insoluble in sodium hydroxide and could be boiled with alkali without decomposition. When warmed for a short time with hydrochloric acid it was converted into the unaltered 2-ethylmercapto-5-benzoylamino-6-oxypyrimidine, melting at 238° – 239° . When it was suspended in dry benzene and the benzene saturated with dry hydrochloric acid gas, the hydrochloride was formed, melting, with violent effervescence, at 147° . When this salt was warmed with water it underwent dissociation and the oxazoline was recovered. Some of the hydrochloric acid salt was heated in a sealed tube, with alcoholic ammonia, for 2 hours, at 100° – 110° . The alcoholic solution was evaporated to dryness and then treated with water, to remove ammonium chloride. The insoluble residue proved to be the unaltered oxazoline, melting at 108° – 109° .

The close relationship between our oxazoline and μ -phenyl-oxazoline, which was prepared by Gabriel and Heyman,¹ is shown by the following formulæ :



NEW HAVEN, CONN.,
May 6, 1905.

¹ Ber. d. chem. Ges., **23**, 2495.



Contributions from the Sheffield Laboratory of Yale University.

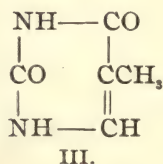
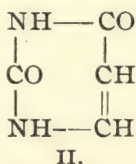
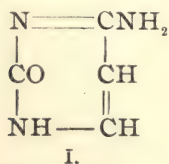
CXXXVII.—RESEARCHES ON PYRIMIDINES: ON 2,5-DIAMINO-6-OXYPYRIMIDINE.

[TWELFTH PAPER.]

BY TREAT B. JOHNSON AND CARL O. JOHNS.

In a paper by Wheeler and Johnson¹ on 5-methylcytosine it was stated that work on the preparation of oxydiaminopyrimidines would be carried on in this laboratory. These particular pyrimidine derivatives are of especial interest because of the fact that Kutscher² believes he isolated such a compound, in the form of its picrate, from yeast nucleic acid. Kutscher considers that a similar analogy exists between his unknown base and cytosine as exists between thymine and uracil. While thymine differs from uracil by a methyl radical, he thinks that his new base differs from cytosine by an amino group.

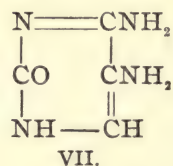
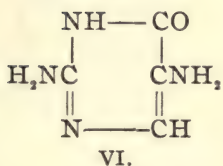
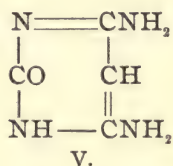
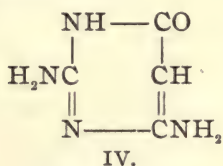
The pyrimidine derivatives that have hitherto been isolated from the decomposition-products of nucleic acid have been mono-oxy or di-oxy derivatives, in which the oxygen atoms occupy position 2 as in cytosine, I., or both positions 2 and 6 as in uracil, II., and thymine, III. :



¹ THIS JOURNAL, 31, 592 (1904).

² Z. physiol. Chem., 38, 176 (1903).

It appears to the writers that if Kutscher's base is an oxydiaminopyrimidine, of all the possible diamino derivatives, the most probable forms to be considered are likewise those in which the oxygen atom occupies either position 2 or 6. An examination of the following formulas will show that the only oxydiamino derivatives that fulfil these conditions, assuming that the amino groups are attached to carbon, are: 6-oxy-2,4-diaminopyrimidine, IV., 2-oxy-4,6-diaminopyrimidine, V., 6-oxy-2,5-diaminopyrimidine, VI., and 2-oxy-5,6-diaminopyrimidine, VII. :



Furthermore, since Kutscher obtained his base by hydrolyzing nucleic acid with sulphuric acid, at a high temperature and under pressure, it is evident that the only forms which need to be considered in the above series are those which are capable of undergoing the same treatment without complete decomposition.

Three of the pyrimidines represented above have now been synthesized: 2,4-diamino-6-oxypyrimidine, IV., has been prepared by Traube.¹ He obtained it by condensing guanidine with ethyl cyanacetate in presence of sodium ethylate. That this derivative cannot be the compound obtained by Kutscher is established by the fact that, when it is heated with 20 to 30 per cent sulphuric acid, at 130°-140°, it is completely decomposed.

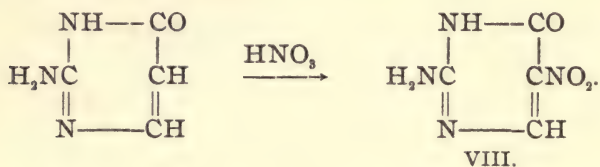
Wheeler and Jamieson² have described 2-oxy-4,6-diamino-

¹ Ber. d. chem. Ges., **33**, 1371.

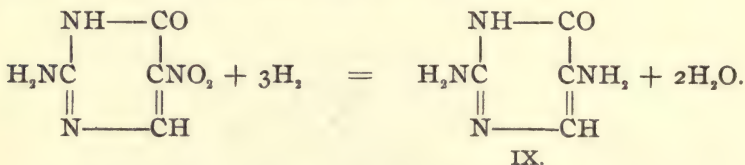
² THIS JOURNAL, **32**, 343 (1904).

pyrimidine, V. Their experimental evidence excludes the possibility of this pyrimidine being identical with Kutscher's base. It was easily hydrolyzed to barbituric acid when boiled with mineral acids.

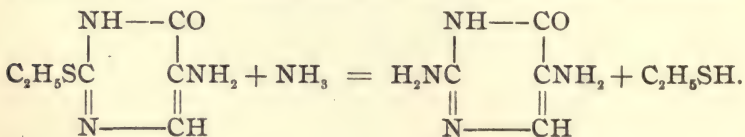
In this paper we shall describe the preparation and properties of the diamino derivative represented by Formula VI., *viz.*: 2,5-diamino-6-oxypyrimidine. We have prepared this pyrimidine by three different methods, as follows: When isocytosine¹ was nitrated in the presence of strong sulphuric acid it was converted, practically quantitatively, into 2-amino-5-nitro-6-oxypyrimidine, VIII. :



When this nitropyrimidine was reduced in an ammoniacal solution with aluminium amalgam, it was converted, smoothly, into 2,5-diamino-6-oxypyrimidine, IX. :



The same pyrimidine was also formed when 2-ethylmercapto-5-amino-6-oxypyrimidine² was heated with alcoholic ammonia.

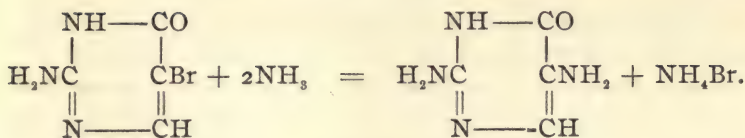


The third method which has served for the preparation of the pyrimidine was by heating bromisocytosine³ with concentrated, aqueous ammonia.

¹ Wheeler and Johnson : *THIS JOURNAL*, **29**, 493 (1903).

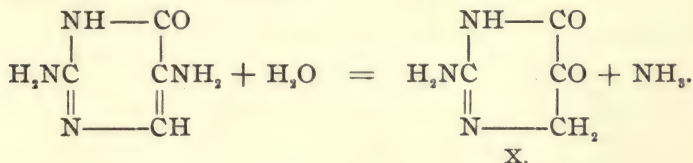
² Johnson : *THIS JOURNAL*, **34**, 191 (1905).

³ Wheeler and Johnson : *Loc. cit.*

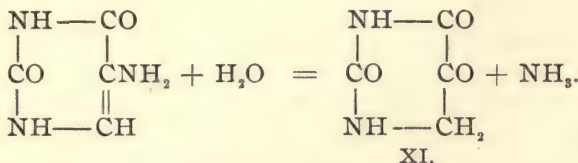


Of the three methods of preparation the first is the only one which is of practical value for the production of the base.

We now find that this 2,5-diamino-6-oxypyrimidine agrees in its chemical behavior, so far as we are able to judge, with the base which Kutscher isolated from yeast. Kutscher's meagre description of his base makes it impossible for us to establish with preciseness the identity of the two compounds. It is the first one of the above series of four pyrimidines which we have been able to heat with sulphuric acid without complete decomposition. Approximately 50 per cent of the pyrimidine was recovered unaltered, after heating with 20 per cent sulphuric acid, at 130°-140°. Part of the base was hydrolyzed by this treatment to a difficultly soluble derivative, which we have identified as 2-amino-5,6-dioxypyrimidine, X. Under the conditions employed in our work we did not observe the formation of aminouracil.



This hydrolysis is perfectly analogous to the formation of oxyuracil, XI., from aminouracil, which was described by Behrend.¹

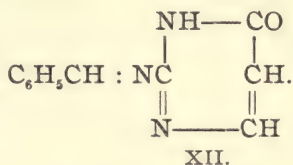


2,5-Diamino-6-oxypyrimidine crystallizes from water with 1

¹ Ann. Chem. (Liebig), 229, 40.

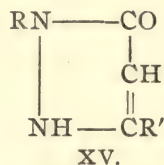
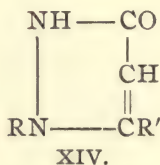
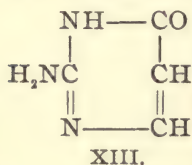
molecule of water of crystallization. Analogous to Kutscher's base it gives a picrate which is extremely insoluble in water. Notwithstanding its insolubility, it is not a derivative suitable for identifying the base on account of its indefinite decomposition-point and poor crystalline form. The base also forms a beautiful crystalline series of salts with nitric, hydrochloric and sulphuric acids.

Especially interesting in connection with the nitration of isocytosine was the behavior of its benzal derivative, XII., towards nitric acid :



While isocytosine nitrates very easily, to give the 2-amino-5-nitro-6-oxypyrimidine, VIII, its benzal derivative could be recovered unaltered after warming with a mixture of nitric acid (sp. gr. 1.5) and concentrated sulphuric acid, for 24 hours.

On account of their close structural relationship, it might be expected that 2-amino-6-oxypyrimidine, XIII, would show some analogy in its chemical behavior to a 3-pyrazolone, XIV., or a 5-pyrazolone, XV. :



Wheeler and Bristol¹ have shown that when pyrimidine derivatives, having hydrogen both in positions 4 and 5, are attacked by halogens or nitric acid, it is the hydrogen atom in position 5 which is substituted. The 3-pyrazolones² and 5-pyrazolones³ are also readily attacked by halogens, the sub-

¹ THIS JOURNAL, 33, 438 (1905).

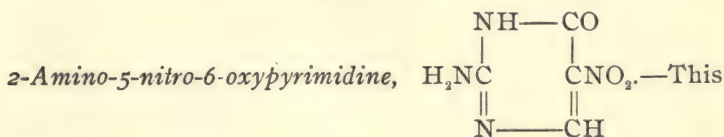
² Ber. d. chem. Ges., 38, 154.

³ Knorr and Duden : *Ibid.*, 25, 766.

stitution taking place in position 4, which corresponds to position 5 in the pyrimidine ring. They also react smoothly, in acetic acid, with sodium nitrite to form characteristic, green-colored nitroso derivatives. We now find isocytosine does not react with nitrous acid; it was recovered unaltered after remaining in a nitrous acid solution for several hours. We did not observe the formation of any uracil.

Work on the preparation of 2-oxy-5,6-diaminopyrimidine is in progress in this laboratory.

EXPERIMENTAL.



nitro derivative was prepared by nitrating isocytosine.¹ After several experiments, in which we used varying proportions of nitric and sulphuric acids, we observed that we obtained the best results when we worked under the following conditions: Six grams of isocytosine were slowly added to a mixture of 18 cc. of nitric acid (sp. gr. 1.5) and 18 cc. of concentrated sulphuric acid. The nitration was very violent and, in order to avoid oxidation, the temperature of the acid mixture was not allowed to rise above 100°. After the final addition of isocytosine the mixture was heated on the steam-bath for 1 hour, to complete the reaction. Longer heating tends to diminish the yield of the nitro product. The acid mixture was thoroughly cooled and poured into 100 cc. of ice-water. The clear yellow solution that resulted was then made slightly alkaline with ammonium hydroxide. On cooling we obtained a beautiful, yellow, crystalline precipitate. It was very difficultly soluble in hot water, from which it separated, on cooling, in clusters of microscopic prisms. It was insoluble in all the ordinary organic media. It was purified for analysis by boiling with glacial acetic acid. It had no definite decomposition point, but began to turn brown at about 280° and did not decompose below 300°. The yield corresponded to 92 per cent

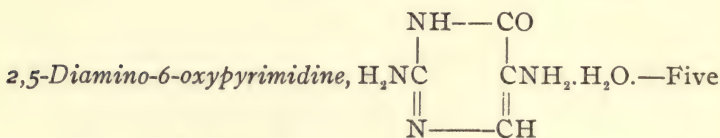
¹ Wheeler and Johnson: *Loc. cit.*

of the theoretical. A nitrogen determination, by Kjeldahl's method, gave :

	Calculated for $C_4H_4O_3N_4$.	Found.
N	35.89	35.70

In order to establish the structure of this nitropyrimidine, it was heated with 20 per cent sulphuric acid, for 4 hours, at 190° – 200° . When the solution was examined a beautiful crystalline solid had separated, which had all the properties of nitrouracil. In order to prove that this was nitrouracil it was reduced to aminouracil with aluminium amalgam, in an ammoniacal solution. That aminouracil was the product of the reduction was established by a determination of nitrogen in the free base and by means of its picrate. The picrate showed signs of decomposing at 147° and then decomposed, with violent effervescence, at 245° – 247° .¹ A determination of nitrogen in the free base gave the following result :

	Calculated for $C_4H_5O_2N_3$.	Found.
N	33.07	32.99



grams of 2-amino-5-nitro-6-oxypyrimidine were suspended in 150 cc. of water, to which 5 cc. of 14 per cent ammonium hydroxide solution had been added. To this ammoniacal solution was then added an excess of aluminium amalgam and the temperature of the solution being kept below 40° during the reduction. The reduction was allowed to proceed for 24 hours, when the aluminium hydroxide was filtered off. We obtained a clear, wine-colored solution, which was concentrated on the steam-bath to about 15 cc. Decomposition took place during this evaporation and a brown, amorphous substance continued to form during prolonged heating. The concentrated solution was filtered and allowed to stand over night. In the morning 1.5 grams of crystalline material had separated. The crystals

¹ Wheeler and Bristol : *THIS JOURNAL*, **33**, 438 (1905).

were badly etched and were developed in the form of large, radiating prisms. Associated with these prisms was a small amount of amorphous material. Some of the large prisms were removed, washed with cold water and dried in the air. The water of crystallization was determined at 120° – 130° .

0.2368 gram substance lost 0.0305 gram.

	Calculated for $C_4H_6ON_4 \cdot H_2O$.	Found.
H_2O	12.50	12.88

The anhydrous base had no definite melting-point. It decomposed, with slow effervescence, at about 245° . Analysis (Kjeldahl):

	Calculated for $C_4H_6ON_4$.	Found.
N	44.44	43.96

2,5-diamino-6-oxypyrimidine is extremely soluble in water. When boiled with water the solution assumes a red color and the base apparently slowly oxidizes, with separation of a flocculent, amorphous residue. It is a strong di-acid base and forms a very characteristic series of salts (see below) with nitric, hydrochloric and sulphuric acids. Of these three salts the nitrate and hydrochloride are very soluble in water. The sulphuric acid salt is difficultly soluble in water and is the most characteristic derivative of the base that we have obtained. The base is precipitated by phosphotungstic acid and mercuric chloride. When solutions of platinum chloride and gold chloride were added to an aqueous solution of the base no double salts separated, but the halides were slowly reduced to metallic platinum and gold. With potassiobismuth iodide the base gives a brick-red precipitate.

The *picrate* was formed when picric acid was added to a dilute, aqueous solution of the base. It was very difficultly soluble in water. It separated from hot water in aggregates of short, distorted prisms (Fig. I.). Traces of impurities modify the crystal forms of the salt. Using a pure sample of the base the picrate separated in the form of stout needles. The picrate had no definite decomposition-point, but decomposed at 250° – 300° , according to the rate of heating. Analysis:

	Calculated for $C_4H_6ON_4 \cdot C_6H_5O_7N_3$.	Found.
N	27.60	27.58

The *dihydrochloride*, $C_4H_6ON_4 \cdot 2HCl \cdot H_2O$, was prepared by dissolving the base in warm, concentrated hydrochloric acid. When the acid solution was allowed to stand the hydrochloride separated in magnificent, prismatic crystals, some of which measured 5 mm. in length. The prisms showed a decided tendency to twin, as shown in Fig. II. The salt contained 1 molecule of water of crystallization, which was determined by heating at 120° - 130° .

0.0896 gram substance lost 0.0077 gram.

	Calculated for $C_4H_6ON_4 \cdot 2HCl \cdot H_2O$.	Found.
H ₂ O	8.29	8.59

Analysis of the anhydrous salt :

	Calculated for $C_4H_6ON_4 \cdot 2HCl$.	Found.
N	28.14	28.07

The *nitrate*, $C_4H_6ON_4 \cdot 2HNO_3$, was obtained by dissolving the base in 20 per cent nitric acid and allowing it to evaporate in a vacuum. It crystallized in beautiful prisms, which were well developed, with very distinct faces (Fig. III.). They were exceedingly soluble in water. The salt did not contain water of crystallization. Analysis :

	Calculated for $C_4H_6ON_4 \cdot 2HNO_3$.	Found.
N	33.3	33.5

The *sulphate*, $C_4H_6ON_4 \cdot H_2SO_4$, was easily obtained when dilute sulphuric acid was added to an aqueous solution of the base. It was very difficultly soluble in water and separated in the form of slender, needle-like prisms. The salt showed a tendency to crystallize in two forms. When deposited from water it usually separated in clusters of radiating needles. When recrystallized from dilute sulphuric acid solution it formed beautiful, long, slender prisms with well-developed faces (Fig. IV.). Neither form contains water of crystallization. Both forms represent the same salt. The salt does not decompose below 300° .



Fig. I.—The picrate of 2,5-diamino-6-oxypyrimidine crystallized from water. Magnified 60 times.

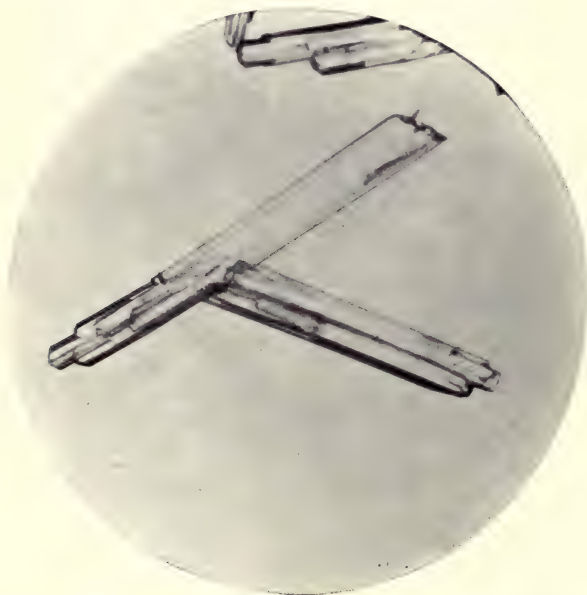


Fig. II.—The hydrochloride of 2,5-diamino-6-oxypyrimidine crystallized from a strong solution of hydrochloric acid. Magnified 60 times.

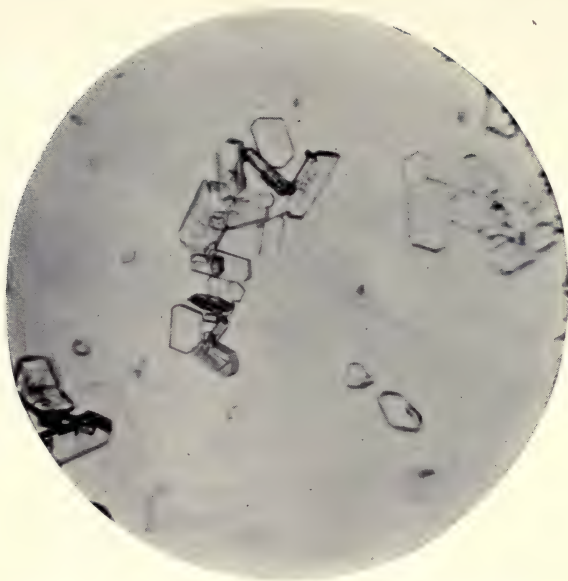


Fig. III.—The nitrate of 2,5-diamino 6-oxypyrimidine crystallized from a strong nitric acid solution. Magnified 60 times.

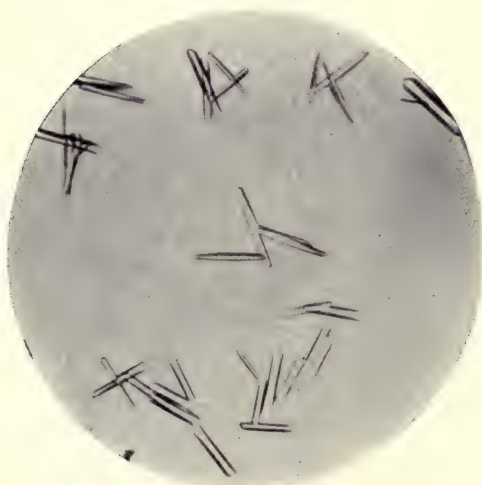


Fig. IV.—The sulphate of 2,5-diamino-6-oxypyrimidine crystallized from dilute sulphuric acid. Magnified 60 times.

Analysis of the needles and prisms of the salt :

N	Calculated for $C_4H_6ON_4.H_2SO_4$.	I.	Found.	II.
	25.00	24.81		24.74

In order to avoid the possibility of dissociation in aqueous solution, solubility determinations of the sulphate were made in normal solutions of sulphuric acid. The solubility was determined by taking exactly 10 cc. of the acid solution, saturated at 25°, and determining the amount of nitrogen present (Kjeldahl). The quantity of salt dissolved in 10 cc. was then calculated from the weight of nitrogen obtained. One hundred cc. of normal sulphuric acid dissolved, at 25° :

I.	II.
0.4928 gram.	0.4704 gram.

While the 2,5-diamino-6-oxypyrimidine apparently undergoes slow decomposition when its aqueous solution is boiled, the sulphate appears to be perfectly stable when subjected to the same treatment. Some of the sulphate was dissolved in 20 per cent sulphuric acid and the solution boiled for about one-half hour. The sulphuric acid was then removed by digesting with pulverized barium carbonate. After filtering from barium carbonate and barium sulphate the filtrate was combined with a solution of picric acid. The picrate that was obtained agreed in all its properties with the picrate of 2,5-diamino-6-oxypyrimidine. Analysis :

N	Calculated for $C_4H_6ON_4.C_6H_3O_7N_3$.	Found.
	27.60	27.66

Behavior of 2,5-Diamino-6-oxypyrimidine when Heated with Sulphuric Acid under Pressure.—This experiment was of especial interest since Kutscher¹ obtained his base by hydrolyzing nucleic acid with sulphuric acid, at a high temperature and under pressure. One gram of the sulphuric acid salt of the pyrimidine base was heated in a sealed tube, with 10 cc. of sulphuric acid, of approximately 20 per cent, for 3 hours, at 130°–140°. There was no pressure when the tube was opened and no apparent decomposition had taken place. The sul-

¹ *Loc. cit.*

phuric acid was removed by digesting with pulverized barium carbonate and, after filtering from barium carbonate and barium sulphate, the filtrate was evaporated over a free flame to about 50 cc. Some of this solution was taken and treated with a cold, saturated solution of picric acid. We obtained an immediate precipitate of a beautiful, crystalline picrate. It was extremely insoluble in water. It separated from hot water in well-developed prisms, which arranged themselves in radiating clusters. The picrate had all the properties of the picrate of 2,5-diamino-6-oxypyrimidine. Analysis (Kjeldahl):

	Calculated for $C_4H_6ON_4 \cdot C_6H_3O_7N_3$.	Found.
N	27.60	27.53

The remaining portion of the above filtrate, after testing for unaltered base with picric acid, was allowed to stand for 2 days, when a small amount of crystalline material separated. It was purified by recrystallizing from water, from which it separated in clusters of microscopic prisms. When heated in a capillary tube the material turned brown, but did not decompose below 300° . A nitrogen determination agreed very closely with the calculated for aminouracil or its isomer, 2-amino-5,6-dioxypyrimidine. The low result obtained was due to the presence of a minute trace of inorganic material ($BaCO_3$?).

	Calculated for $C_4H_5O_2N_3$.	Found.
N	33.0	32.4

In order to distinguish between aminouracil and 2-amino-5,6-dioxypyrimidine, the base was dissolved in hot water and treated with a saturated solution of picric acid. The picrate separated in the form of microscopic prisms. It showed no signs of decomposing at 147° . It charred at 240° – 250° , but did not effervesce below 280° . Aminouracil decomposes at 247° with violent effervescence.¹

Action of Ammonia on Bromisocytosine or 2-Amino-5-brom-6-oxypyrimidine.—Three grams of bromisocytosine² were heated

¹ Wheeler and Bristol: *Loc. cit.*

² Wheeler and Johnson: *Loc. cit.*

with an excess of aqueous ammonia, for 6 hours, at 190° – 215° . When the tube was opened the solution was perfectly clear and no resin had separated. The solution gave a heavy precipitate of silver bromide when treated with nitric acid and silver nitrate. The ammoniacal solution was evaporated over a free flame to remove the excess of ammonia. On continued evaporation the solution gradually assumed a deep wine color and a slimy deposit slowly formed on the surface of the liquid. After the excess of ammonia was removed the solution was filtered and combined with a solution of picric acid, which yielded a very insoluble picrate. It was poorly crystallized and showed no definite decomposition-point. It gave no test for bromine. A nitrogen determination agreed with that calculated for the picrate of 2,5-diamino-6-oxypyrimidine.

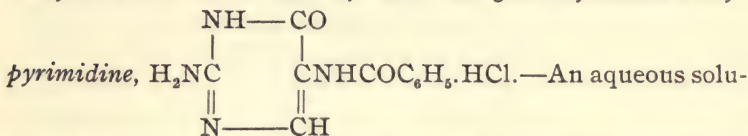
	Calculated for $C_4H_6NO_4 \cdot C_6H_3O_7N_3$.	Found.
N	27.60	28.10

*Action of Ammonia on 2-Ethylmercapto-5-amino-6-oxypyrimidine.*¹—When 2-ethylmercapto-5-amino-6-oxypyrimidine was heated in a sealed tube, with an excess of concentrated aqueous ammonia, at 131° – 142° , for 4 hours it was recovered unaltered. It was again heated for 3 hours, at 180° – 190° . Under these conditions only a trace of mercaptan was detected and again unaltered material was obtained. Three grams of the mercapto derivative were then heated for 4 hours, at 200° – 205° , with strong alcoholic ammonia. When the tube was opened there was slight pressure and a strong odor of mercaptan. A small amount of slimy, insoluble residue had also separated. The solution was filtered and evaporated to dryness. We obtained a red-colored oil, which showed no signs of solidifying. It was dissolved in water and boiled with animal charcoal to remove the color. When the clarified solution was treated with picric acid we obtained a picrate which was difficultly soluble in water. It gave no test for sulphur and decomposed at 250° – 300° , according to the rate of heating. A nitrogen determination agreed with the calculated for the picrate of 2,5-diamino-6-oxypyrimidine.

¹ Johnson : *Loc. cit.*

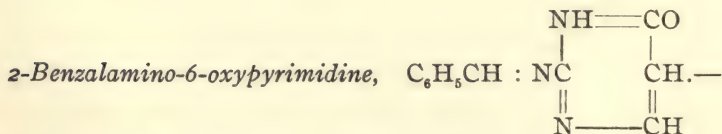
	Calculated for $C_4H_6ON_4.C_6H_5O_7N_3.$	Found.
N	27.60	27.71

Hydrochloric Acid Salt of 2-Amino-5-benzoylamino-6-oxy-



tion of guanidine was prepared by dissolving 25 grams of guanidine carbonate in water and then adding an aqueous solution containing a molecular proportion of barium hydroxide. The barium carbonate was filtered off and to the solution was added 50 grams of the sodium salt of ethyl formylhippurate. The solution was then heated on the steam-bath for 1-2 hours. The clear liquid was made distinctly acid with sulphuric acid and concentrated to about one-half its volume. Upon cooling, nothing separated. The solution was now treated with a slight excess of mercuric chloride, when a white mercury salt was obtained. This was washed with water and decomposed with hydrogen sulphide. On evaporating the filtrate, after filtering from mercuric sulphide and cooling, a crystalline product was obtained. It was insoluble in alcohol, but crystallized from hot water in microscopic needles. It contained chlorine and decomposed with violent effervescence at about 275° . We did not obtain a sufficient amount of the salt to isolate the free base. Analysis (Kjeldahl) :

	Calculated for $C_{11}H_{11}O_2N_4Cl.$	Found.
N	21.01	21.04



Five grams of isocytosine were heated at 160° - 180° , for 3 hours, with a molecular proportion of benzaldehyde. Water was given off and a yellow, crystalline cake was obtained. It

was insoluble in water and alcohol. It showed both acid and weak basic properties. It dissolved in ammonia to a deep red solution. Its salts undergo dissociation in aqueous solution. Some of the material was dissolved in 20 per cent sulphuric acid and filtered while hot into cold water. The base was precipitated at once as a yellow, crystalline solid. After washing with water and alcohol, it decomposed at 238° – 242° . Analysis :

	Calculated for $C_{11}H_9ON_3$.	Found.
N	21.10	21.11

The following experiments illustrate the remarkable stability of this pyrimidine towards nitric acid: Eight and one-half grams of the crude material were dissolved in a mixture of 20 cc. of nitric acid (sp. gr. 1.5) and 15 cc. of concentrated sulphuric acid. The mixture was warmed on the steam-bath for 3 hours and then allowed to stand for 24 hours at 40° – 60° . We obtained a clear, red solution. When the acid solution was poured into water a crystalline product separated which was identified as a mixture of the unaltered benzal derivative and some metanitrobenzaldehyde. After boiling with alcohol, to remove the nitrobenzaldehyde, the benzalaminopyrimidine was obtained, melting at about 242° . When mixed with the pure material the melting-point was not altered. When the benzal derivative was again heated with a mixture of nitric acid (sp. gr. 1.5) and concentrated sulphuric acid, at 90° – 100° , no nitro-product was obtained but a violent oxidation took place and the pyrimidine was completely decomposed.

Action of Nitrous Acid on Isocytosine.—Four grams of isocytosine were dissolved in acetic acid. Into this solution was introduced solid sodium nitrite and the liquid allowed to stand over night, at the ordinary temperature. In the morning a crop of microscopic prisms had separated. When fused on platinum foil they left no inorganic residue. The material was very soluble in cold water. It turned brown at about 280° , but did not melt at 300° . A nitrogen determination agreed with that calculated for an acetic acid salt of isocytosine.

N	Calculated for $C_6H_9O_3N_3$ 24.56	Found. 24.26
NEW HAVEN, CONN., June 7, 1905.		

I.—RESEARCHES ON PYRIMIDINS: SOME 5-IODOPYRIMIDIN DERIVATIVES; 5-IODOCYTOSIN.

PLATE I.

(Thirteenth Paper.)

By TREAT B. JOHNSON AND CARL O. JOHNS.

(Contributions from the Sheffield Laboratory of Yale University.)

(Received for publication, December 19, 1905.)

The object of the work described in this paper was to prepare some 5-iodopyrimidin derivatives and investigate their behavior towards ammonia and organic bases. It was considered desirable to compare the reactivity of such iodine derivatives with that of the analogous bromine compounds. In the course of our work on pyrimidins, it was necessary to decide whether 5-iodopyrimidins might serve for syntheses in which the bromine derivatives could not be used.

Several iodine-substituted pyrimidins have been described in the literature,¹ but so far as the writer is aware no attempts have hitherto been made to prepare iodine derivatives by direct iodation. We have selected for our investigation three pyrimidin derivatives, in which the 4- and 5-positions are occupied by hydrogen, viz.: 2-ethylmercapto-6-oxypyrimidin,² (I); 2,6-dioxypyrimidin³ (Uracil, II.); and 2-oxy-6-amino-pyrimidin⁴ (Cytosin, III). Wheeler and Bristol have shown that when such pyrimidins⁵ are attacked by nitric acid or bromine it is the hydrogen atom occupying the 5-position that is substituted. It might be expected that they would be attacked by iodine in a similar manner to form the corresponding 5-iodopyrimidins.

We now find that the three pyrimidins selected can be con-

¹ Gabriel and Colman, *Ber. d. deutsch. chem. Gesellsch.*, xxxii, p. 1525, 1899; *ibid.*, xxxii, p. 2921, 1899; Emery, *ibid.*, xxxiv, p. 4178, 1901; Büttner, *ibid.*, xxxvi, p. 2227, 1903.

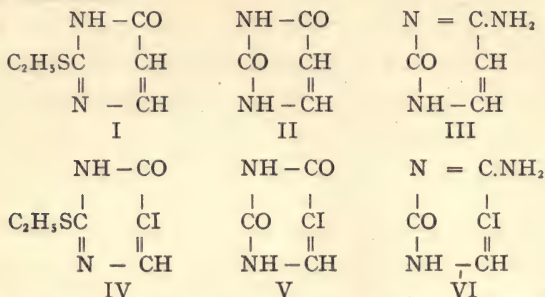
² Wheeler and Merriam, *Amer. Chem. Jour.*, xxix, p. 484, 1903.

³ Wheeler and Merriam, *loc. cit.*

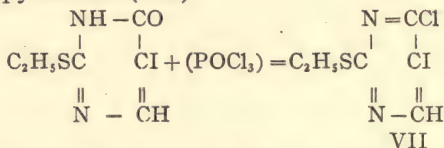
⁴ Wheeler and Johnson, *ibid.*, xxix, p. 492, 1903.

⁵ *Ibid.*, xxxiii, p. 437, 1905.

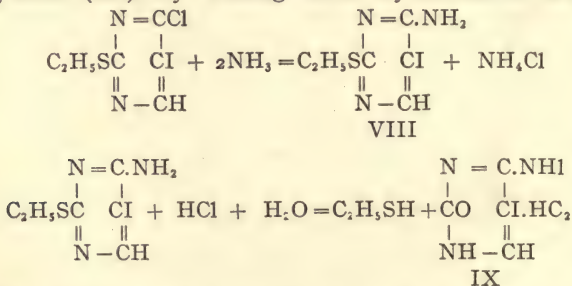
verted smoothly into 5-iodopyrimidins if treated with iodine in an alkaline solution.



In order to show that the iodine enters the pyrimidin ring in the same position (5) we have furthermore prepared 5-iodocytosin (VI) from 2-ethylmercapto-5-iodo-6-oxypyrimidin (IV). When this compound was warmed with phosphorus oxychloride it was converted quantitatively into 2-ethylmercapto-5-iodo-6-chlorpyrimidin (VII).



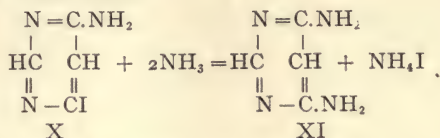
When this chlorpyrimidin was heated with alcoholic ammonia it reacted quantitatively to form 2-ethylmercapto-5-iodo-6-aminopyrimidin (VIII). This was then converted into 5-iodocytosin (IX) by boiling with hydrochloric acid. This



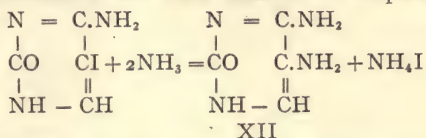
synthesis supports the assumption that the iodine in these compounds occupies the 5- and not the 4-position. Büttner¹ has shown that when an iodine occupies the 4-position in a

¹ *Loc. cit.*

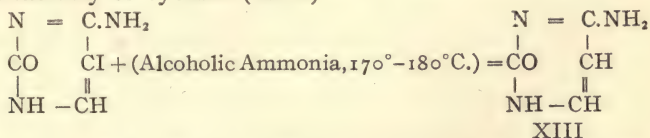
pyrimidin, it behaves as an imide-chloride, and can be replaced by an amino-radical. He prepared 4, 6-diaminopyrimidin (XI) by heating the corresponding 4-iodo-6-aminopyrimidin (X) with alcoholic ammonia.



It was of especial interest to investigate the behavior of 5-iodocytosin (VI) towards ammoniacal solutions, since it offered a possibility of preparing 2-oxy-5, 6-diamino-pyrimidin (XII). Furthermore we had reason to expect that 5-iodo-



cytosin (VI) would not show the same behavior towards aqueous and alcoholic ammonia. Johnson and Johns¹ have shown that such ammoniacal solutions show a remarkable difference in their reactivity. We now find that this iodo-pyrimidin (VI) can be heated with concentrated aqueous ammonia and be recovered unaltered. This result is in accord with an observation made by Wheeler and Johnson² in their examination of the properties of the corresponding 5-bromcytosin. On the other hand when 5-iodocytosin was heated with strong alcoholic ammonia under the same conditions with respect to temperature and time of heating, it was reduced practically quantitatively to cytosin (XIII).

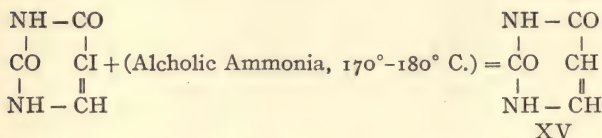
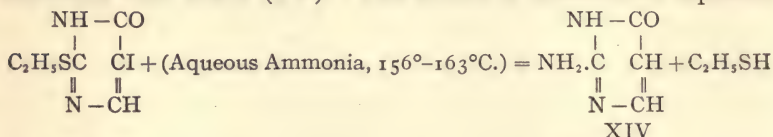


We now find that 2-ethylmercapto-5-iodo-6-oxypyrimidin (IV) and 5-iodouracil (V) likewise show a remarkable difference in behavior towards aqueous and alcoholic ammonia solutions. The mercaptopyrimidin (IV) can be heated with alcoholic am-

¹ *Ibid.*, xxxiv, p. 175, 1905.

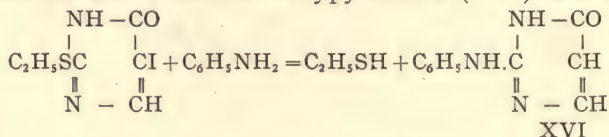
² *Ibid.*, xxxi, p. 591, 1904.

monia and recovered unaltered. On the other hand when heated with concentrated aqueous ammonia at the same temperature mercaptan was evolved and it was converted into 2-amino-6-oxypyrimidin (Isocytosin, XIV). 5-Iodouracil reacted in a reverse manner. When heated with aqueous ammonia it was recovered unaltered. On the other hand it was converted by alcoholic ammonia into uracil (XV). The action of alcoholic or aqueous



ammonia on 2-ethylmercapto-5-brom-6-oxypyrimidin¹ at temperatures between 140° and 200° C. does not give smooth results. Merriam² has shown that 5-bromuracil is converted smoothly into 5-amino-uracil when heated with aqueous ammonia.

We have observed that this replacement of iodine by a hydrogen atom can take place in the presence of aniline as well as ammoniacal solutions. When 2-ethylmercapto-5-iodo-6-oxypyrimidin (IV) was heated with aniline at 100° C., mercaptan was evolved and 2-anilino-6-oxypyrimidin (XVI) was formed.

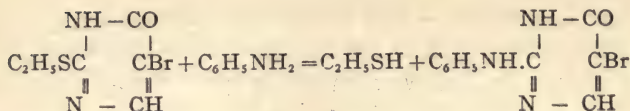


The same anilino-pyrimidin was obtained when 2-ethylmercapto-6-oxypyrimidin (I) was heated with aniline at 100° C. This abnormal result again illustrates the difference in behavior between 5-iodopyrimidins and their bromine analogues. The corresponding 2-ethylmercapto-5-brom-6-oxypyrimidin reacts quantitatively with aniline at 100° C. to form 2-anilino-5-brom-6-oxypyrimidin,³

¹ Wheeler and Johnson, *loc. cit.*

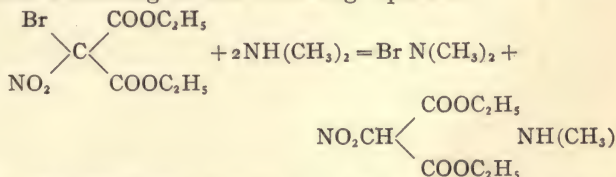
² *Amer. Chem. Jour.*, xxxi, p. 603, 1904.

³ Wheeler and Bristol, *ibid.*, xxxiii, p. 444, 1905.



It is a remarkable fact that the reduction of 2-ethylmercapto-5-iodo-6-oxypyrimidin to 2-ethylmercapto-6-oxypyrimidin should take place at a much lower temperature with aniline than with ammonia. In our experiments with iodocytosin we did not observe the formation of cytosin when it was heated with aniline. It was recovered unaltered after heating with aniline from 190° to 200° C.

We are not inclined to consider these abnormal replacements of iodine by hydrogen as exceptional cases of reduction. It seems probable to the writer that the mechanism of these interesting reactions is analogous to that when diethylbromnitromalonate is treated with amines. This ester was investigated by Willstätter and Hottenroth¹ in their attempts to synthesize Drechsel's diamino-acetic acid.² They observed that the bromine atom in this ester was extremely loosely bound, and it was reduced to diethylnitromalonate when treated with ammonia or fatty amines. They showed that it reacted with dimethylamine according to the following equation:



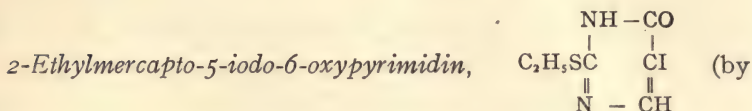
The ease with which the iodine in 2-ethylmercapto-5-iodo-6-oxypyrimidin (IV) could be replaced by hydrogen in the presence of amines suggested that this iodopyrimidin, under certain conditions, might be used for syntheses in reactions involving double decomposition. We now find that under the conditions employed in our experiments the iodine was very firmly bound and could not be replaced. For example: It could be heated with the potassium salt of phthalimid in alcohol, or with the sodium salt of urethane in benzene at 160° C. and be recovered unaltered. In these experiments it shows the stability of the corresponding

¹ Ber. d. deutsch. chem. Gesellsch., xxxvii, p. 1775, 1904.

² Beilstein, Handbuch, i, p. 1194.

bromine derivative — 2-ethylmercapto-5-brom-6-oxypyrimidin. This compound and also 2-ethylmercapto-5-brom-6-amino-pyrimidin¹ could be heated with the potassium salt of phthalimid at 200° C. without any evidence of the formation of potassium bromide.

EXPERIMENTAL PART.

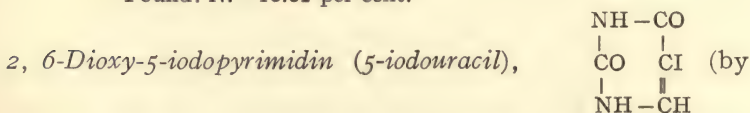


Dr. J. G. Statiropulos).—Ten grams of 2-ethylmercapto-6-oxypyrimidin,² were dissolved in 50 c.c. of water containing 3 grams of sodium hydroxide. To this solution was then slowly added 17 grams of pulverized iodine. After all the iodine had been added the solution was warmed on the steambath until the free iodine dissolved. The iodopyrimidin separated from the hot solution. After acidifying with acetic acid the solution was filtered and the pyrimidin purified by crystallization from alcohol. It deposited in slender prisms, arranged in crosses, and melted at 196° C. to a clear oil. It was insoluble in water, and readily soluble in benzene. The yield was practically quantitative. Analysis:

For $\text{C}_6\text{H}_7\text{ON}_2\text{SI}$ —

Calculated: N = 9.93 per cent.

Found: N. = 10.02 per cent.



Dr. J. G. Statiropulos).—This compound was easily obtained when uracil was dissolved in alkali and treated with iodine as in the preparation of the above 2-ethylmercapto-5-iodo-6-oxypyrimidin. It crystallized from hot water in glistening scales, and decomposed at 272° C. It was soluble in hot alcohol. Analysis:

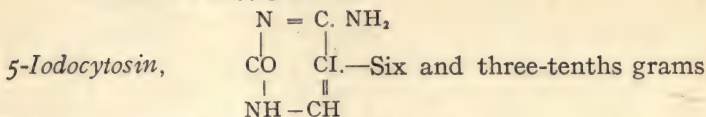
¹ Wheeler and Johnson, *loc. cit.*

² Wheeler and Merriam, *loc. cit.*

For $C_4H_3O_2N_2I$ —

Calculated: N = 11.86 per cent.

Found: N = 11.77 per cent.



of synthetical cytosin¹ were dissolved in about 50 c.c. of water containing 3.3 grams of potassium hydroxide. To this solution were slowly added, with frequent shaking, 14.5 grams of finely pulverized iodine. The reaction was smooth and the iodocytosin began to separate immediately. After all the iodine had been added the solution was warmed on the steambath for a few minutes to complete the reaction. After neutralizing the free alkali with acetic acid the base was filtered off and recrystallized from boiling water. It separated on cooling in characteristic, branched crystals (Figure 1), which decomposed between 225° and 245° C. without effervescence, giving off iodine vapors.

It was practically insoluble in alcohol and benzene. The yield was quantitative. Analysis (Kjeldahl):

0.1188 gm. of substance gave 0.0210 gm. of nitrogen = 15 c.c. of $\frac{N}{10}$ HCl.

For $C_4H_4ON_3I$ —

Calculated: N = 17.72 per cent.

Found: N = 17.67 per cent.

Solubility of iodocytosin in water: One liter of water at 25° C. dissolved (1) 0.936 gram, (2) 0.988 gram.

Iodocytosin is very stable in the presence of boiling hydrochloric acid. One gram of the base was boiled with concentrated hydrochloric acid for two hours. The acid solution was then evaporated to dryness and the residue treated with a little dilute ammonia. We obtained the unaltered base which decomposed at from 220° to 235° C. Analysis (Kjeldahl):

0.1210 gm. of substance gave 0.02142 gm. of nitrogen = 15.3 c.c. $\frac{N}{10}$ HCl.

For $C_4H_4ON_3I$ —

Calculated: N = 17.72 per cent.

Found: N = 17.70 per cent.

Picrate of iodocytosin: The picrate crystallized from hot water in long needles. It had no definite melting point but

¹ Wheeler and Johnson, *loc. cit.*

decomposed with effervescence at from 247° to 257° C. according to the rate of heating. Analysis (Kjeldahl):

0.1705 gm. of substance gave 0.03066 gm. of nitrogen = 21.9 c.c. $\frac{N}{10}$ HCl

For $C_4H_4ON_3I \cdot C_6H_5O_7N_3$ —

Calculated: N = 18.02 per cent.

Found: N = 17.98 per cent.

Acetic acid salt of iodocytosin: This salt is of special interest on account of its dissociation in a hot solution of acetic acid. Some iodocytosin was dissolved in hot acetic acid and the solution divided into two equal parts. The first part was then cooled quickly, when the unaltered base immediately separated in the form of irregular prisms. Analysis (Kjeldahl):

0.1253 gm. of substance gave 0.02198 gm. of nitrogen = 15.7 c.c. $\frac{N}{10}$ HCl.

For $C_4H_4ON_3I$ —

Calculated: N = 17.72 per cent.

Found: N = 17.54 per cent.

The second part was allowed to stand for several hours. The unaltered base separated at first in distorted prisms. On standing these prisms slowly assumed a new form and were transformed into large well developed prisms with distinct faces (Figure 2). They became opaque at about 110° C., and decomposed at from 220° to 240° C. according to the rate of heating. A nitrogen determination agreed with the calculated percentage in the acetic acid salt (Kjeldahl):

0.1320 gm. of substance gave 0.0189 gm. of nitrogen = 13.5 c.c. $\frac{N}{10}$ HCl.

0.1029 gm. of substance gave 0.01456 gm. of nitrogen = 10.4 c.c. $\frac{N}{10}$ HCl.

For $C_6H_8O_3N_3I$ —

Calculated: N = 14.14 per cent.

Found: N = (1) 14.31; (2) 14.15 per cent.

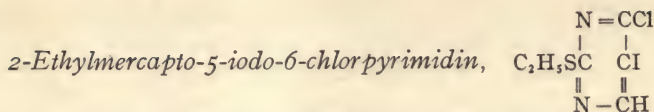
In order to decide whether the salt would dissociate again, it was dissolved in hot acetic acid and the solution cooled. The base was again obtained in the form of irregular prisms. Analysis (Kjeldahl):

0.0811 gm. of substance gave 0.01428 gm. of nitrogen = 10.2 c.c. $\frac{N}{10}$ HCl.

For $C_4H_4ON_3I$ —

Calculated: N = 17.72 per cent

Found: N = 17.60 per cent.



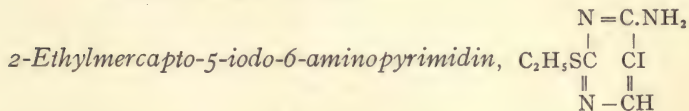
This compound was prepared by warming on the steambath 20 grams of 2-ethylmercapto-5-iodo-6-oxypyrimidin with 50 c.c. of phosphorus oxychloride. After the evolution of hydrochloric acid ceased the excess of phosphorus oxychloride was removed by heating at 100° C. under a pressure of 50 millimeters of mercury. We obtained a thick, brown varnish which immediately solidified when triturated with ice water. This contained iodine and melted at 68° C. to a turbid oil. It was purified by crystallizing from petroleum ether. It deposited in large prisms and melted at 69° C. to a clear oil. The yield was 20 grams, or 95 per cent. of the theoretical. Analysis (Kjeldahl):

0.2050 gm. of substance gave 0.01918 gm. of nitrogen = 13.7 c.c. $\frac{\text{N}}{16}$ HCl.

For $\text{C}_6\text{H}_6\text{N}_2\text{SClI}$ —

Calculated: N = 9.32 per cent.

Found: N = 9.35 per cent.



This compound was obtained when 10 grams of 2-ethylmercapto-5-iodo-6-chlorpyrimidin were heated with alcoholic ammonia for three hours at 128°–130° C. When the tube was examined the base had crystallized from the alcoholic solution in long, slender prisms. The crude material melted at 126° C. When allowed to crystallize slowly from alcohol it deposited in slender prisms that arranged themselves in clusters radiating from a common center. It melted at 127° C. The yield was quantitative. Analysis (Kjeldahl):

0.1368 gm. of substance gave 0.02044 gm. of nitrogen = 14.6 c.c. $\frac{\text{N}}{16}$ HCl.

For $\text{C}_6\text{H}_8\text{N}_3\text{SI}$ —

Calculated: N = 14.94 per cent.

Found: N = 14.94 per cent.

When 5 grams of this amino-pyrimidin were boiled with concentrated hydrochloric acid for one hour mercaptan was evolved

and it was converted practically quantitatively into 5-iodocytosin. Analysis (Kjeldahl):

0.1386 gm. of substance gave 0.02422 gm. of nitrogen = 17.3 c.c. $\frac{N}{10}$ HCl.

For $C_8H_8ON_3I$ —

Calculated: N = 17.72 per cent.

Found: N = 17.47 per cent.

2-Ethylmercapto-5-iodo-6-anilino-pyrimidin, $C_{12}H_{12}N_2SCl$

$$\begin{array}{c} N=C.NHC_6H_5 \\ | \quad | \\ SC-Cl \\ || \quad || \\ N-CH \end{array}$$

was obtained by warming a benzene solution of 2 grams of 2-ethylmercapto-5-iodo-6-chlorpyrimidin and 1.4 grams of aniline. After evaporating the excess of benzene and washing with water to dissolve aniline hydrochloride, the base was obtained as an oil which would not solidify. It was purified by converting it into its sulphuric acid salt. This crystallized from alcohol, which contained sulphuric acid, in well developed prisms. The sulphate had no definite melting point but decomposed above 200° C. A nitrogen determination (Kjeldahl) agreed with the calculated value for a normal sulphate:

0.0923 gm. of substance gave 0.00938 gm. of nitrogen = 6.7 c.c. $\frac{N}{10}$ HCl.

For $(C_{12}H_{12}N_2SI)_2H_2SO_4$ —

Calculated: N = 10.34 per cent.

Found: N = 10.17 per cent.

2-Anilino-6-oxypyrimidin, $C_8H_8N_2O$

$$\begin{array}{c} NH-CO \\ | \quad | \\ C-CH \\ || \quad || \\ N-CH \end{array}$$

— This compound

was prepared by warming on the steambath 2-ethylmercapto-6-oxypyrimidin with the calculated quantity of aniline. It was also formed when an alcoholic solution of the mercaptopyrimidin and aniline were digested for several hours. It was moderately soluble in alcohol, and insoluble in benzene and water. It was purified for analysis by crystallization from alcohol. It deposited in well developed plates and melted at 230°–231° C. to a yellow oil. Analysis:

For $C_{10}H_8ON_2$ —

Calculated: N = 22.46 per cent.

Found: N = 22.54 per cent.

Action of Aniline on 2-Ethylmercapto-5-iodo-6-oxypyrimidin.—Fifteen grams of the iodopyrimidin were heated on the steambath

with 25 grams of aniline for six hours. It dissolved in the warm aniline to give a clear solution which gradually assumed a dark blue color. After the evolution of mercaptan ceased, the excess of aniline was removed by distillation with steam. We obtained a dark crystalline product that was insoluble in water. It was washed with cold alcohol to remove the coloring matter and purified by repeated crystallizations from alcohol and acetic acid. It failed to respond to tests for iodine and sulphur. It melted at 230° – 231° C. to a yellow oil. It agreed in all its properties with 2-anilino-6-oxypyrimidin (M. P. 230° – 231° C.). A mixture of the two compounds melted sharply at 230° – 231° C. Analyses for carbon, hydrogen, and nitrogen gave the following results:

0.0845 gm. of substance gave 16.7 c.c. nitrogen gas at 20° C. and 768 mm.

0.2491 gm. of substance gave 0.1193 gm. of H_2O and 0.5881 gm. of CO_2 .

Calculated for $C_{10}H_5ON_3$ —

Found—

C	64.2 per cent	64.4 per cent
H	4.8 " "	5.3 " "
N	22.46 " "	22.8 " "

Action of Aniline on 2-Ethylmercapto-5-iodo-6-aminopyrimidin.

—This pyrimidin was recovered unaltered after heating with aniline for nine hours at 100° C. It melted at 127° C. and when mixed with the original material the melting point was not lowered.

Action of Aniline on 5-Iodocytosin.—This base was recovered unaltered after heating with aniline, in benzene, for one hour at 150° – 160° C. The temperature was then raised to 190° – 193° C., and maintained for two hours. When the tube was examined there was no evidence that any reaction had taken place. The iodocytosin was again recovered unaltered.

Action of Aqueous Ammonia on 2-Ethylmercapto-5-iodo-6-oxypyrimidin.—Five grams of the pyrimidin were heated with concentrated aqueous ammonia for three hours at 156° to 163° C. When the tube was examined the solution had assumed a red color and drops of mercaptan were floating on the surface of the liquid. The solution gave a strong test for iodine. The ammoniacal solution was evaporated to dryness. We obtained a crystalline residue that was soluble in water except a small amount of white crystalline material. This was identified as

the unaltered 2-ethylmercapto-5-iodo-6-oxypyrimidin. It melted at 196°C . and gave a strong test for iodine. The aqueous filtrate was concentrated on the steambath and combined with a strong solution of picric acid. We obtained a beautiful yellow picrate that crystallized from hot water in prisms. It had no definite melting point but decomposed above 260°C . and effervesced violently at about 285°C . It did not contain water of crystallization. It contained neither iodine nor sulphur. A nitrogen determination agreed with the calculated value for 2-amino-6-oxypyrimidin (XIV) (Isocytosin). Analysis:

0.1229 gm. of substance gave 0.03052 gm. of nitrogen = $21.8\text{ c.c. } \frac{\text{N}}{10}\text{ HCl}$.

For $\text{C}_4\text{H}_5\text{ON}_3 \cdot \text{C}_6\text{H}_3\text{O}_7\text{N}_3$ —

Calculated: N = 24.70 per cent.

Found: N = 24.83 per cent.

Action of Alcoholic Ammonia on 2-Ethylmercapto-5-iodo-6-oxypyrimidin.—After heating the pyrimidin with alcoholic ammonia for six hours at 141° to 148°C . it was recovered unaltered. It was then heated for six hours at 150° to 155°C . Under these conditions only a trace of mercaptan was detected. The contents of the tube were evaporated to dryness. We obtained a crystalline residue. This was insoluble in water and after one crystallization from alcohol it melted at 195°C . It contained both sulphur and iodine. When mixed with the original 2-ethylmercapto-5-iodo-6-oxypyrimidin the melting point was not altered. We did not detect the presence of any isocytosin.

Action of Alcoholic Ammonia on 5-Iodocytosin.—Five grams of iodocytosin were heated with strong alcoholic ammonia for six hours at 170° to 180°C . When the tube was opened considerable decomposition had taken place, and a well crystallized product was suspended in the alcohol. It crystallized from hot water in plates. It did not melt below 300°C . and contained no iodine. It contained one molecule of water of crystallization and agreed in all its properties with *cytosin*. Analysis:

0.2711 gm. of substance lost 0.0372 gm. of H_2O at 110° – 120°C .

For $\text{C}_4\text{H}_5\text{ON}_3 \cdot \text{H}_2\text{O}$ —

Calculated: H_2O = 13.95 per cent.

Found: H_2O = 13.72 per cent.

0.0909 gm. of anhydrous base gave 0.0343 gm. of nitrogen = $24.5\text{ c.c. } \frac{\text{N}}{10}\text{ HCl}$.

For $C_4H_5ON_3$ —

Calculated: N = 37.84 per cent.

Found: N = 37.73 per cent.

Action of Aqueous and Alcoholic Ammonia on 5-Iodouracil.—When iodouracil was heated with concentrated aqueous ammonia at 170° – 180° C. for four hours it was recovered unaltered. Some of the pyrimidin was then heated with strong alcoholic ammonia under the same conditions. When the tube was examined slight decomposition had taken place and a colorless compound was suspended in the alcohol. It crystallized from hot water in balls of microscopic prisms and did not melt below 300° C. More of the same material was obtained when the alcoholic solution was concentrated. It did not contain iodine and was identified as uracil. The yield was practically quantitative. We did not detect the presence of any amino-uracil. Analysis (Kjeldahl):

0.1192 gm. of substance gave 0.02982 gm. of nitrogen = 21.3 c.c. $\frac{N}{10}$ HCl.

0.0757 gm. of substance gave 0.0189 gm. of nitrogen = 13.5 c.c. $\frac{N}{10}$ HCl.

For $C_4H_4O_2N_2$ —

Calculated: N = 25.00 per cent.

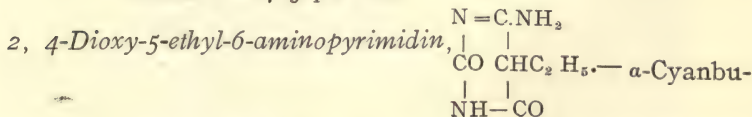
Found: N = (1) 25.01; (2) 24.96 per cent.

α -Cyanbutyrylurea, $CH_3 \cdot CH_2 \cdot CH(CN) \cdot CO \cdot NH \cdot CO \cdot NH_2$.—This compound was obtained by condensing α -cyanbutyric acid with urea. We proceeded according to the directions given by Traube¹ for the preparation of cyanacetylurea from cyanacetic acid and urea. It crystallized from water in arborescent crystals and melted at 181° C. with slight effervescence. Analysis:

For $C_6H_9O_2N_3$ —

Calculated: N = 27.1 per cent.

Found: N = 27.5 per cent.



tyrylurea dissolved in 33 per cent. sodium hydroxide solution with absorption of heat. Fourteen grams of the urea were dissolved in 42 grams of the alkali solution and allowed to stand for several hours at ordinary temperature. The solution was then neutralized with hydrochloric acid. We obtained a

¹ Ber. d. deutsch. chem. Gesellsch., xxxiii, p. 1371, 1900.

beautiful crystalline product that decomposed at 325° – 330° C. with violent effervescence. It crystallized from hot water in needle-like prisms and decomposed at 339° C. with effervescence (using an Anschutz thermometer). It was soluble in hydrochloric acid, and was reprecipitated unaltered with ammonia.

Analysis:

For $C_6H_5O_2N_3$ —

Calculated: N = 27.1 per cent.

Found: N = 26.9 per cent.

DESCRIPTION OF PLATE I.

Figure 1. 5-Iodocytosin, crystallized from hot water. Magnified 60 times.

Figure 2. The acetic acid salt of 5-iodocytosin. Magnified 60 times.



FIGURE 1.

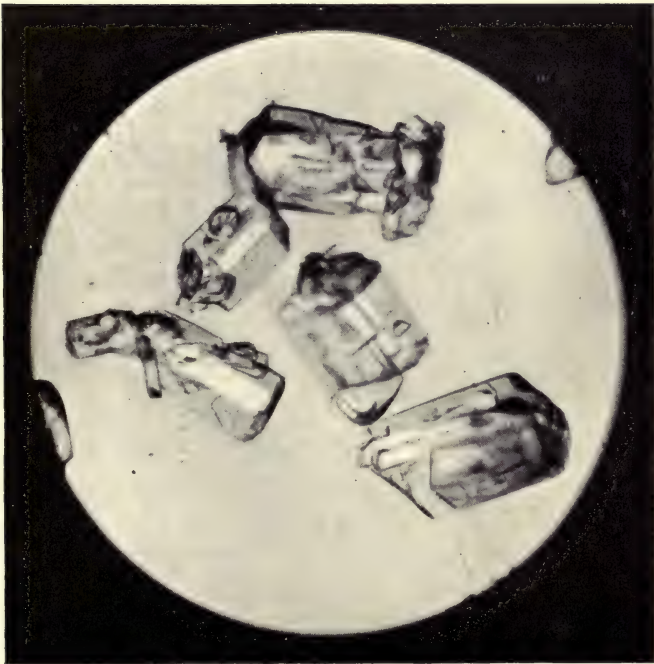


FIGURE 2.

II. RESEARCHES ON PYRIMIDINS: ON METHODS OF SYNTHESIZING ISOBARBITURIC ACID, AND 5-OXY-CYTOSIN.

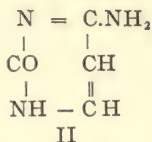
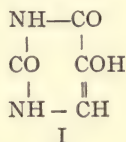
(Fourteenth Paper.)

By TREAT B. JOHNSON AND ELMER V. McCOLLUM.

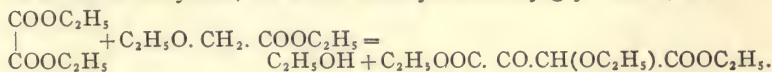
(From the Sheffield Laboratory of Yale University.)

(Received for publication, January 2, 1906.)

In this paper we describe a new synthesis of isobarbituric acid, I. In the course of the work we have also prepared several new derivatives of this acid and of cytosin, II, which are of especial interest.

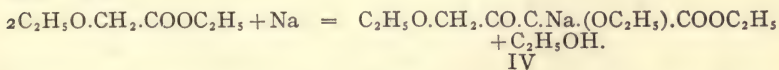


Wislicenus and Scheidt¹ have shown that diethyloxalate condenses with the ethyl ester of ethylglycollic acid, in presence of sodium ethylate, to form diethyloxaethylglycollate, III.



III

It was also observed by Conrad² that diethylglycollate undergoes an inner condensation, in benzene, in the presence of metallic sodium to form the sodium salt of ethyl α, γ -diethoxyacetoacetate³, IV.



IV

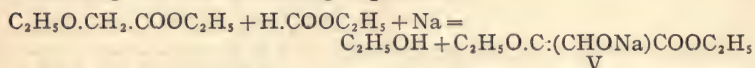
It might be expected that ethylformate would also condense

¹ Ber. d. deutsch. chem. Gesellsch., xxiv, p. 432, 1891.

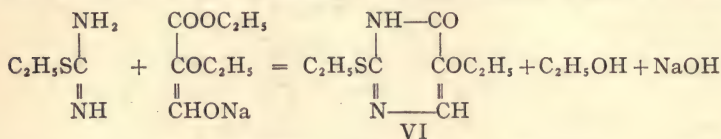
² Ibid., xi, p. 58, 1878.

³ Ann. d. Chem. (Liebig), cclxix, p. 28, 1892.

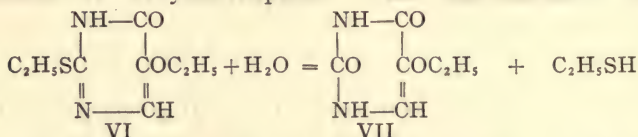
with diethylglycollate in the presence of metallic sodium to form the sodium salt of ethyl- α -ethoxy- β -oxyacrylate,¹ V. We find that this condensation takes place in the normal manner according to the following equation:



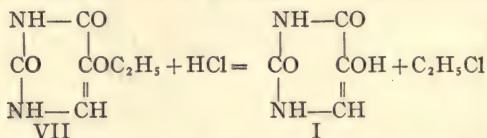
When this sodium salt, V., was dissolved in water with the calculated quantity of pseudoethylthiourea they reacted to form 2-ethylmercapto-5-ethoxy-6-oxypyrimidin, VI., as follows :



This mercaptopyrimidin, VI., was converted practically quantitatively into isobarbituric acid, I., when heated with hydrochloric acid. This change involves two distinct reactions, as follows: The 2-ethylmercapto-5-ethoxy-6-oxypyrimidin, VI., is first converted into 2,6-dioxy-5-ethoxypyrimidin, VII., with evolution of ethylmercaptan. This intermediate ethoxy-



pyrimidin, VII., then reacts with hydrochloric acid to give isobarbituric acid, I., with formation of ethylchloride.

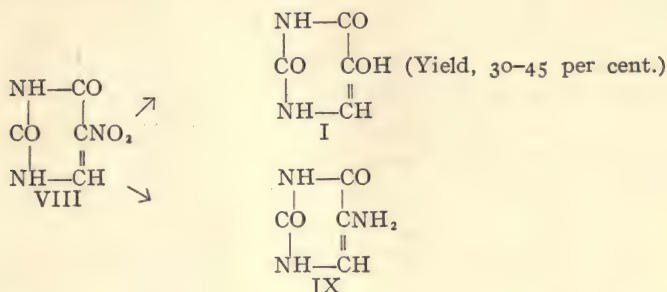


The only method, given in the literature, for preparing isobarbituric acid is that described by Behrend.² He prepared it by reducing nitrouracil, VIII., with tin and hydrochloric acid.

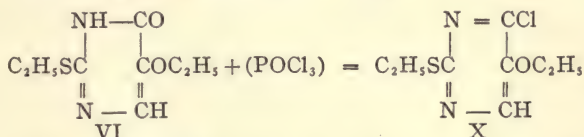
¹We find that ethylformate condenses with ethylphenoxyacetate— $\text{C}_6\text{H}_5\text{O}.\text{CH}_2.\text{COOC}_2\text{H}_5$ —to give a quantitative yield of the sodium salt of ethyl- α -phenoxy- β -oxyacrylate— $\text{C}_6\text{H}_5\text{O}.\text{C}:(\text{CHONa}).\text{COOC}_2\text{H}_5$. We shall condense ethylformate with other glycollic esters and study some of the reactions of this new class of substituted acrylic esters. (T. B. J.)

²*Ann. d. Chem.* (Liebig), ccxxix, p. 39; Behrend and Roosen, *ibid.*, ccli, p. 239.

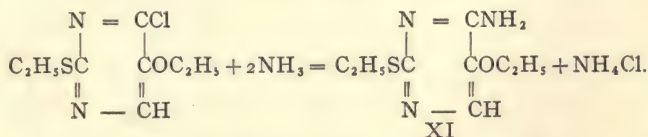
This method of preparation is not suitable for preparing large quantities of the acid. Part of the nitrouracil is recovered in the form of a minouracil, IX., and the yield of isobarbituric acid, I., corresponds to only about thirty to forty-five per cent. of the theoretical.



When 2-ethylmercapto-5-ethoxy-6-oxypyrimidin, VI., was warmed with phosphorus oxychloride, it was converted smoothly into 2-ethylmercapto-5-ethoxy-6-chlorpyrimidin, X.



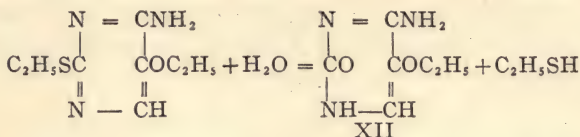
This chlorpyrimidin, X., gave a theoretical yield of 2-ethylmercapto-5-ethoxy-6-aminopyrimidin, XI., when heated with strong alcoholic ammonia:



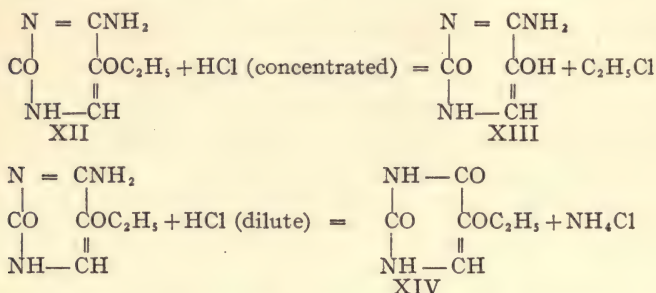
Especially interesting was the behavior of this aminopyrimidin, XI., towards hydrochloric acid. When heated with this reagent, it was converted into isobarbituric acid. We have investigated the mechanism of this reaction and find that it involves the formation of several intermediate compounds. We have succeeded in isolating each intermediate product of the reaction.

2-Ethylmercapto-5-ethoxy-6-aminopyrimidin, XI., is first

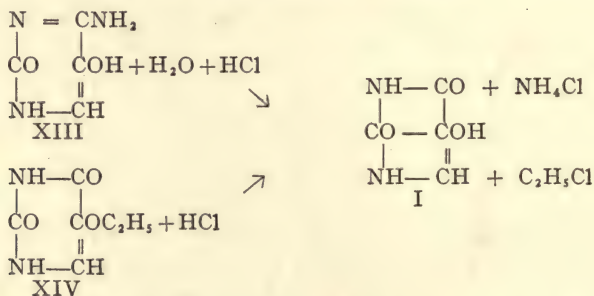
converted into 2-oxy-5-ethoxy-6-aminopyrimidin or 5-*ethoxycytosin*, XII.



5-Ethoxycytosin, XII., then reacts in two ways, according to the strength of the hydrochloric acid used, giving 2,5-dioxy-6-aminopyrimidin or 5-*oxycytosin*, XIII., and 2,6-dioxy-5-ethoxypyrimidin, XIV., as follows:



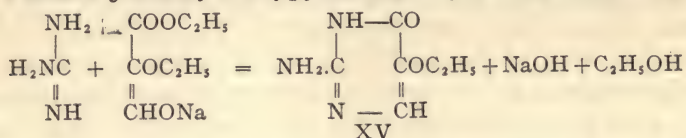
5-Oxycytosin, XIII., and 2,6-dioxy-5-ethoxypyrimidin, XIV., then react with an excess of hydrochloric acid to form isobarbituric acid according to the following equations:



The sodium salt of ethyl- α -ethoxy- β -oxyacrylate, V., can also be used for preparing 5-oxy-derivatives of isocytosin.¹ Dr. C. O. Johns finds that this salt condenses with guanidin to

¹Wheeler and Johnson, *Amer. Chem. Jour.*, xxix, p. 492, 1903.

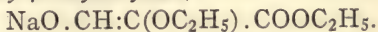
give 2-amino-5-ethoxy-6-oxypyrimidin or 5-ethoxyisocytosin, XV.



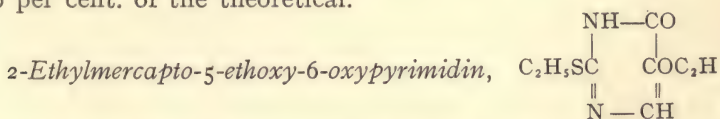
We shall continue the study of these interesting pyrimidin derivatives in this laboratory.

EXPERIMENTAL PART.

Sodium Salt of Ethyl- α -ethoxy- β -oxyacrylate,



This salt was prepared by slowly adding to ether, in which was suspended the calculated quantity of sodium, a mixture of molecular proportions of ethylformate and the ethyl ester of ethylglycolic acid. The condensation proceeded smoothly with evolution of hydrogen gas. In the course of 8 to 12 hours, the sodium all dissolved. We made no attempts to isolate the sodium salt. It was hygroscopic and very soluble in ether. After the condensation was complete, the excess of ether was evaporated in a partial vacuum and the crude salt dissolved in water. This aqueous solution was used for experiments that we describe in this paper. We have assumed, for the purpose of calculation, that the yield of sodium salt corresponds to about 90 per cent. of the theoretical.



This pyrimidin was prepared as follows: 80 grams of the hydrobromic acid salt of pseudoethylthiourea were dissolved in about 150 c.c. of cold water and added to a strong aqueous solution containing two molecular proportions of the sodium salt of ethyl- α -ethoxy- β -oxyacrylate. This solution was then combined with 50 c.c. of water containing a molecular proportion of potassium hydroxide (24.5 grams). The mixture was then thoroughly shaken; allowed to stand one hour at ordinary temperature, and then heated on the steam-bath for another hour. It was then thoroughly cooled and acidified with acetic acid. An excess of acetic acid should be avoided as the pyrim-

idin is somewhat soluble in this reagent. The mercaptopyrimidin separated at once as a brown, crystalline product. The crude material melted at 160° – 165° C. The yield was 50 grams, or 61 per cent. of the theoretical, calculating from the weight of pseudothiourea used. This yield of pyrimidin was not increased when we used more than a one-half molecular proportion of the hydrobromic acid salt of the pseudothiourea for the condensation. Long standing of the alkaline solution also does not increase the yield of pyrimidin. In one experiment the solution was divided into three equal parts and treated as follows: one part was warmed immediately on the steam-bath for one hour and then acidified with acetic acid; the second part was allowed to stand two hours, and the third twenty-four hours before warming on the steam-bath and acidifying with acetic acid. The yields of pyrimidin from the three equal portions were practically the same. The pyrimidin is difficultly soluble in hot water and practically insoluble in the cold. It deposited from hot alcohol in rhombic-shaped prisms and melted at 169° C. to a clear oil. Analysis (Kjeldahl) :

0.4170 gram of substance gave 0.05712 gram of nitrogen = 40.8 c.c. $\frac{1}{10}$ normal HCl.

Calculated for $C_8H_{12}O_2N_2S$:	Found.
N = 14.00 per cent.	13.70 per cent.

Action of Hydrochloric Acid on 2-Ethylmercapto-5-ethoxy-6-oxy-pyrimidin.—The mercapto-radical in this pyrimidin is very firmly bound and cannot be removed in the usual manner by boiling with hydrochloric acid. The mercaptopyrimidin was recovered unaltered after boiling for several hours with this acid. It was also recovered unaltered (melting at 168° C.) after boiling with redistilled hydrobromic acid for six hours.

Action of Twenty Per Cent. Hydrochloric Acid at 150° C.—Ten grams of the mercaptopyrimidin were heated with an excess of twenty per cent. hydrochloric acid for four hours at 150 – 155° C. When the tube was opened there was considerable pressure due to the presence of ethylchloride and ethylmercaptan floated on the surface of the liquid. A colorless, crystalline product was suspended in the solution. It was insoluble in cold water. It deposited from hot water in the form of balls of microscopic prisms. It had no definite decomposition point and did not contain sulphur. A nitrogen determination indicated a mixture

of isobarbituric acid and 2, 6-dioxy-5-ethoxypyrimidin. Analysis (Kjeldahl):

0.1363 gram of substance gave 0.02646 gram of nitrogen = 18.9 c.c. $\frac{1}{10}$ normal HCl.

Calculated for $C_4H_4O_3N_2$.	Calculated for $C_6H_8O_3N_2$.	Found.
N = 21.87 per cent.	17.92 per cent.	19.3 per cent.

We did not have enough material to separate the ethoxy-derivative sufficiently pure for analysis. In order to separate the isobarbituric acid from any ethoxy-derivative the mixture was dissolved in boiling acetic anhydride. Upon cooling the acetyl-derivative¹ of isobarbituric acid was obtained in the form of well-developed prisms. It crystallized from hot water in the form of radiating prisms. Analysis (Kjeldahl):

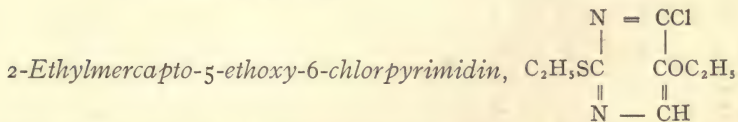
0.1162 gram of substance gave 0.01897 gram of nitrogen = 13.55 c.c. $\frac{1}{10}$ normal HCl.

Calculated for $C_6H_6O_4N_2$.	Found.
N = 16.47 per cent.	16.33 per cent.

Action of Concentrated Hydrochloric Acid at 150° C.—When the mercaptopyrimidin was heated with concentrated hydrochloric acid, it was converted smoothly into isobarbituric acid. Four grams of the mercaptopyrimidin were heated with concentrated hydrochloric acid for three hours at 145° to 155° C. When the tube was opened there was great pressure (ethylchloride) and ethylmercaptan was recognized by its stench. The solution was evaporated to dryness to remove the excess of hydrochloric acid. The crystalline residue was then purified for analysis by repeated recrystallizations from hot water. It separated in corpuscular crystals and decomposed above 300° C., without melting. A nitrogen determination agreed with the calculated in isobarbituric acid.

0.0590 gram of substance gave 0.01288 gram of nitrogen = 9.2 c.c. $\frac{1}{10}$ normal HCl.

Calculated for $C_4H_4O_3N_2$.	Found.
N = 21.87 per cent.	21.83 per cent.



Thirty grams of 2-ethylmercapto-5-ethoxy-6-oxypyrimidin

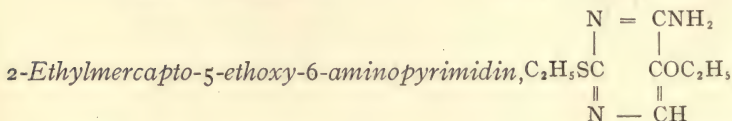
¹ Behrend and Roosen, *loc. cit.*

were warmed with 50 c. c. of phosphorus oxychloride. Hydrochloric acid began to be evolved immediately, and after heating a few minutes on the steam-bath the reaction was complete. The excess of phosphorus oxychloride was then removed by heating at 100° C. under diminished pressure. We obtained a double compound of phosphorus oxychloride and the chlorpyrimidin that was not decomposed by cold water. It was insoluble in water and did not solidify on standing. In order to isolate the chlorpyrimidin it was necessary to decompose the phosphorus compound with hot water. By this treatment the chlorpyrimidin was obtained as an oil which finally solidified. It was dissolved in ether; the ethereal solution dried over calcium chloride and purified by distillation under diminished pressure. Almost the entire product boiled constant at 185° C. under a pressure of 25 millimeters. On cooling, it crystallized in beautiful, radiating prisms which melted at 44°–46° C. It crystallized from ligroin in well developed prisms that melted at 46° C. The chloride could be boiled with water for hours without any apparent change. It was soluble in cold alcohol and benzene. The yield of distilled product was 24 grams or 73 per cent. of the theoretical. Analysis (Kjeldahl):

0.2446 gram of substance gave 0.0368 gram of nitrogen = 22. c. c. $\frac{1}{10}$ normal HCl.

0.1605 gram substance gave 18.9 c. c. nitrogen gas at 24° and 757 mm.

Calculated for $C_8H_{11}ON_2SCl$.	Found.	
	I.	II.
N = 12.81 per cent.	12.59	13.1 per cent.



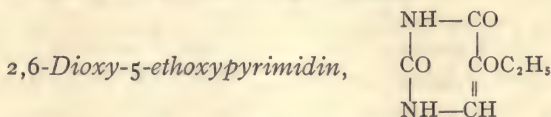
Fourteen grams of 2-ethylmercapto-5-ethoxy-6-chlorpyrimidin were heated with an excess of concentrated alcoholic ammonia for three hours at 150°–160° C. Under these conditions the aminopyrimidin was obtained as a well crystallized solid. It was insoluble in cold water and alcohol. It deposited from hot water or alcohol in rhombic-shaped prisms that melted at 105° C. to a clear oil. The yield was quantitative. When we attempted to prepare this base by heating with alcoholic ammonia

at 120°–130° C. about one-half of the chlorpyrimidin was recovered unaltered. Analysis:

Calculated for $C_5H_7ON_3S$.
N = 21.10 per cent.

Found.
21.00 per cent.

Action of Twenty Per Cent. Hydrochloric Acid on 2-Ethylmercapto-5-ethoxy-6-aminopyrimidin:

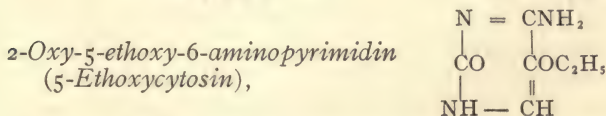


Three grams of the aminopyrimidin were heated in a sealed tube with an excess of 20 per cent. hydrochloric acid for four hours at 150°–160° C. When the tube was examined there was little pressure and drops of mercaptan were suspended in the liquid. The solution was filtered and allowed to evaporate spontaneously in a vacuum. After about three-fourths of the liquid had evaporated, a small amount of crystalline material separated. This was filtered off and crystallized from hot water. It deposited in balls of microscopic prisms and agreed in its behavior with that of isobarbituric acid. We did not obtain sufficient material for analysis. The acid filtrate was evaporated on the steam-bath to about 10 c.c. On cooling, a well-crystallized product deposited. This was filtered off and the filtrate saved (see 5-ethoxycytosin.) It crystallized from hot water in aggregates of radiating prisms. It began to turn brown at about 220° C. and then decomposed from 260° to 280° C. with effervescence according to the rate of heating. It was insoluble in acids and did not respond to a test for sulphur. Analysis (Kjeldahl):

0.0881 gram of substance gave 0.01617 gram of nitrogen = 11.5 c. c. $\frac{1}{10}$ normal HCl.

Calculated for $C_6H_8O_3N_2$.
N = 17.94 per cent

Found.
18.3 per cent.



The acid filtrate, after filtering from the 2, 6-dioxy-5-ethoxypyrimidin described above, was allowed to evaporate to dryness at ordinary temperature. There remained a crystalline residue

which dissolved in cold water to a clear solution. When this was made distinctly alkaline with ammonium hydroxide, we obtained a beautiful deposit of slender prisms. They melted sharply at 300° C. to a black oil. The compound was very soluble in warm water. It was free from sulphur and did not contain water of crystallization. Analysis:

Calculated for $C_6H_9O_2N_3$.
N = 27.09 per cent.

Found.
27.22 per cent.

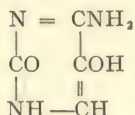
Picrate of 5-Ethoxycytosin.—This was obtained when picric acid was added to a solution of the base. It deposited in characteristic, arborescent crystals. When slowly heated, it melted at 229° – 231° C. to a clear oil. Analysis:

Calculated for $C_6H_9O_2N_3 \cdot C_6H_3O_7N_3$.
N = 21.87 per cent.

Found.
22.00 per cent.

Action of Concentrated Hydrochloric Acid on 2-Ethylmercapto-5-ethoxy-6-aminopyrimidin.

2, 5-Dioxy-6-aminopyrimidin (5-Oxycytosin)



Three grams of 2-ethylmercapto-5-ethoxy-6-aminopyrimidin were heated in a sealed tube with concentrated hydrochloric acid at 150° C. for two hours. When the tube was opened there was great pressure (ethylchloride) and a strong odor of ethylmercaptan. The contents of the tube were evaporated on the steam-bath to a syrup and then dissolved in 10 c.c. of cold water. When this aqueous solution was made alkaline with ammonia we obtained a crystalline precipitate. It was purified by first boiling with alcohol to remove any unaltered mercaptopyrimidin and then crystallizing from water. It deposited in prismatic crystals that did not melt below 280° C. On account of the small amount obtained of the base, we were unable to free it from impurities. Nevertheless a nitrogen determination indicated that we were dealing with a 2, 5-dioxy-6-aminopyrimidin:

Calculated for $C_4H_5O_2N_3$.
N = 33.0 per cent.

Found.
32.20 per cent.

This experiment was repeated under the following conditions: Five grams of the mercaptopyrimidin were heated with concentrated hydrochloric acid for three hours at 150° – 160° C. Ethylchloride and ethylmercaptan were formed as in the previous

experiment. The contents of the tube were evaporated to dryness on the steam-bath. We obtained a crystalline residue that partly dissolved in cold water. The insoluble material was filtered off and crystallized from hot water. It was difficultly soluble and deposited on cooling in balls of microscopic prisms. It had no definite melting point and did not contain sulphur. A nitrogen determination agreed with the calculated value in isobarbituric acid.

Calculated for $C_4H_4O_3N_2$.
N = 21.87 per cent.

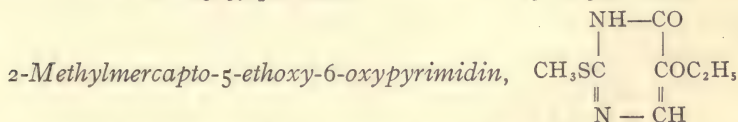
Found.
22.3 per cent.

The aqueous filtrate above, after filtering from isobarbituric acid, was made alkaline with ammonium hydroxide. We obtained no precipitate at first, but after a few hours microscopic prisms deposited which were identified as isobarbituric acid. The alkaline solution was again filtered and then combined with a strong solution of picric acid. We obtained a well-crystallized picrate. It deposited from hot water in well-developed prisms arranged in crosses. When heated in a capillary tube it sintered above $220^\circ C.$, then slowly decomposed above $240^\circ C.$ but did not effervesce at $270^\circ C.$ It was free from sulphur and did not contain water of crystallization. A nitrogen determination agreed with the calculated value in the picrate of 2,5-dioxy-cytosin (Kjeldahl):

0.1067 gram of substance gave 0.02506 gram of nitrogen = 17.9 c.c. $\frac{1}{10}$ normal HCl.

Calculated for $C_4H_5O_2N_3 \cdot C_6H_5O_7N_3$.
N = 23.59 per cent.

Found.
23.48 per cent.



Seventy-five grams of the hydriodic acid salt of pseudomethylthiourea were dissolved in water and added to a solution of 120 grams of the sodium salt of ethyl- α -ethoxy- β -oxyacrylate. To this solution was then added a molecular proportion of potassium hydroxide (19.5 grams) which was first dissolved in water. The mixture was then allowed to stand for four hours; warmed on the steam-bath for one hour, and then acidified with acetic acid. The solution was then concentrated to about one-half its original volume and thoroughly cooled. The

mercapto-pyrimidin deposited in the form of prisms. The yield of crude material was 40 grams. It was insoluble in cold water. It crystallized from hot alcohol or water in stout prismatic crystals that melted at 190° C. to a clear oil. Analysis (Kjeldahl):

0.1811 gram of substance gave 0.02667 gram of nitrogen = 19.05 c.c. $\frac{1}{10}$ normal HCl.

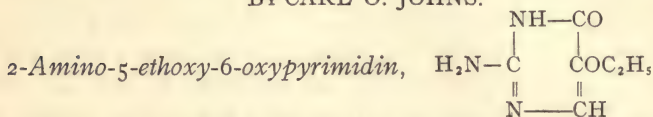
Calculated for $C_7H_{10}O_2N_2S$.

N = 15.05 per cent.

Found.

14.73 per cent.

By CARL O. JOHNS.



Eighty-two grams of guanidin carbonate were dissolved in water and combined with a solution of 150 grams of barium hydroxide. The barium carbonate was filtered off and the clear filtrate containing guanidin was added to an aqueous solution of 90 grams of the sodium salt of ethyl- α -ethoxy- β -oxyacrylate. The mixture was then allowed to stand for twenty-four hours. When it was neutralized with acetic acid no precipitate was obtained. The solution was then concentrated on the steam-bath and the base precipitated with a cold, saturated solution of mercuric chloride. This was filtered off, washed with cold water, and decomposed with hydrogen sulphide. The mercury sulphide was removed by filtration and the clear filtrate evaporated to dryness. We obtained a dark colored residue which was dissolved in water and boiled with animal charcoal to remove the color. When this solution was neutralized with ammonia, the pyrimidin base separated in the form of distorted prisms. It formed a very insoluble sulphate that crystallized from hot, dilute sulphuric acid in well developed prisms. They decomposed at 225° – 226° C. with effervescence and contained two molecules of water of crystallization:

0.8588 gram of substance lost 0.0700 gram of H_2O at 110° – 120° C.

Calculated for $(C_6H_9O_2N_3)_2 \cdot \text{H}_2\text{SO}_4 \cdot 2\text{H}_2\text{O}$. Found.

H_2O = 8.11 per cent.

8.18 per cent.

Nitrogen determination in the hydrous salt (Kjeldahl): 0.1037 gram of salt gave 0.01960 gram of nitrogen = 14 c.c. $\frac{1}{10}$ normal HCl.

Calculated for $(C_6H_9O_2N_3)_2 \cdot \text{H}_2\text{SO}_4 \cdot 2\text{H}_2\text{O}$. Found.

N = 18.9 per cent.

18.9 per cent.

Nitrogen determination in the anhydrous salt (Kjeldahl): 0.1255

gram of salt gave 0.02548 gram of nitrogen = 18.2 c.c. $\frac{1}{10}$ normal HCl.

Calculated for $(C_6H_9O_2N_3)_2 \cdot H_2SO_4$. Found.

N = 20.58 per cent.

20.31 per cent.

The pyrimidin base was isolated in a pure state when this sulphuric acid salt was digested in water with barium carbonate. The excess of barium carbonate and barium sulphate was removed by filtration and the filtrate evaporated to dryness. The base was obtained in the form of distorted prisms. It deposited from hot water in microscopic prisms which melted at 248° C. to a clear oil. Analysis (Kjeldahl):

0.0978 gram of substance gave 0.02618 gram of nitrogen = 18.7 c.c. $\frac{1}{10}$ normal HCl.

Calculated for $C_6H_9O_2N_3$.

Found.

N = 27.09 per cent.

26.77 per cent.



Contributions from the Sheffield Laboratory of Yale University.

CXXXI.—RESEARCHES ON PYRIMIDINES : THE AC-
TION OF POTASSIUM THIOCYANATE UPON
IMIDE CHLORIDES.

[FIFTEENTH PAPER.]

BY TREAT B. JOHNSON AND ELMER V. MCCOLLUM.

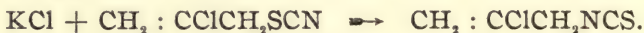
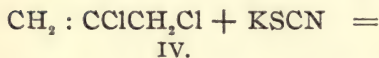
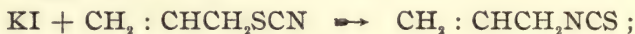
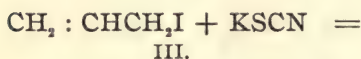
We shall describe in this paper a new case of the molecular rearrangement of a thiocyanate, I., to an isothiocyanate, II., which is unique for this type of metamerism.



In the acyclic series an unsaturated condition in the 2,3-position



is favorable for the formation of isothiocyanates. For example: Allyliodide, III., and 1,2-dichlorpropylene,¹ IV., when heated with potassium thiocyanate, react to form the corresponding isothiocyanates, according to the following equations :

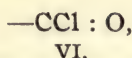
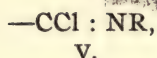


Such groupings, so far as examined, do not permit of the isolation of the primary products—thiocyanates—except when heat is avoided.

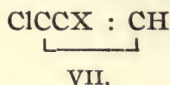
In a recent publication from this laboratory, Wheeler and Bristol² have described the behavior of some cyclic imide chlorides towards potassium thiocyanate. Since such chlorides, V., are closely related to acid chlorides, VI., and the cyclic

¹ Wheeler and Merriam : J. Am. Chem. Soc., 23, 287.

² THIS JOURNAL, 33, 448 (1905).

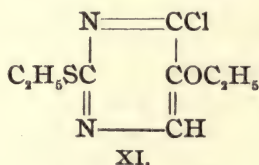
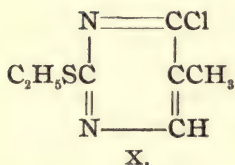
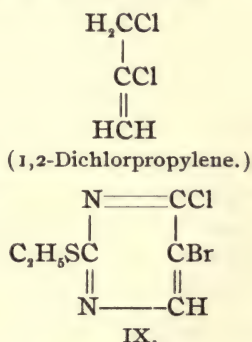
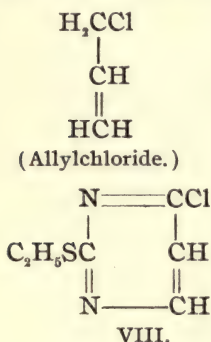


derivatives examined contain an unsaturated 2,3-position, VII.,



it seemed probable that isothiocyanates would result if such halides were treated with potassium thiocyanate.

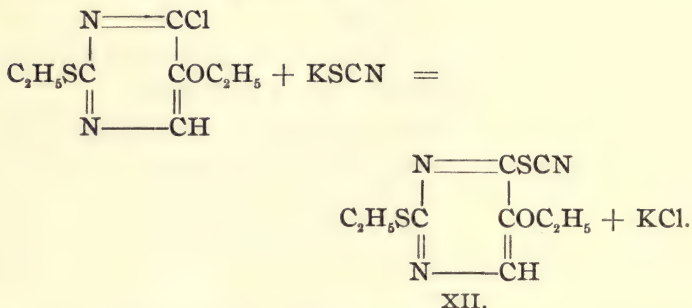
Their experimental data supported this assumption. They observed that 2-ethylmercapto-6-chlorpyrimidine, VIII., 2-ethylmercapto-5-brom-6-chlorpyrimidine, IX., and 2-ethylmercapto-5-methyl-6-chlorpyrimidine, X., reacted with potassium thiocyanate, under certain conditions, to give the corresponding isothiocyanates. They did not obtain any positive evidence of the intermediate formation of thiocyanates :



We had occasion to examine, in the course of our work, the behavior of 2-ethylmercapto-5-ethoxy-6-chlorpyrimidine,¹ XI., towards potassium thiocyanate. On account of the close analogy of this imide chloride to those examined by Wheeler

¹ Johnson and McCollum : J. Biol. Chem., **1**, 437 (1906).

and Bristol,¹ we expected that it would react in a similar manner to form an isothiocyanate. We find that this chloride, XI., reacts smoothly with potassium thiocyanate, in an alcoholic solution, to give a normal rhodanide, XII., as represented in the following equation :



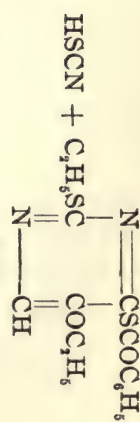
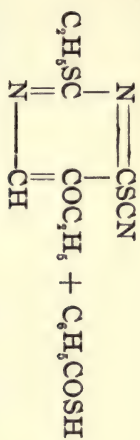
That a thiocyanate is the primary product of this reaction, we have established in the following manner: It did not give thiourea derivatives with ammonia or organic bases. It reacted quantitatively with thiobenzoic and thioacetic acids to give the same 2-ethylmercapto-5-ethoxy-6-thiopyrimidine, XIV. This reaction with thioacids involves the intermediate formation of 2-ethylmercapto-5-ethoxy-6-benzoylmercaptopyrimidine, XIII., and 2-ethylmercapto-5-ethoxy-6-acetylmercaptopyrimidine,² XV., which then undergo hydrolysis to the thiopyrimidine, XIV.

We find that 2-ethylmercapto-5-ethoxy-6-thiocyanpyrimidine, XII., shows no tendency to rearrange to the isothiocyanate,³ XVI., at the ordinary temperature. On the other hand, if heated above 100° it is transformed quantitatively into its isomer, XVI. The thiocyanate can be recrystallized from alcohol, but on prolonged boiling it partially rearranges to the isothiocyanate. This combines at once with the alcohol to form a urethane, XVII.

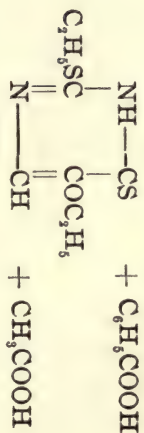
¹ *Loc. cit.*

² Wheeler and Merriam: *THIS JOURNAL*, 23, 283 (1901).

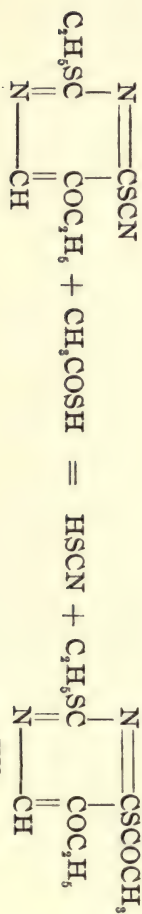
³ Samples of the thiocyanate that had been preserved for five months showed no change in melting point. We shall keep specimens for an indefinite period in order to see whether any rearrangement will take place at the ordinary temperature.



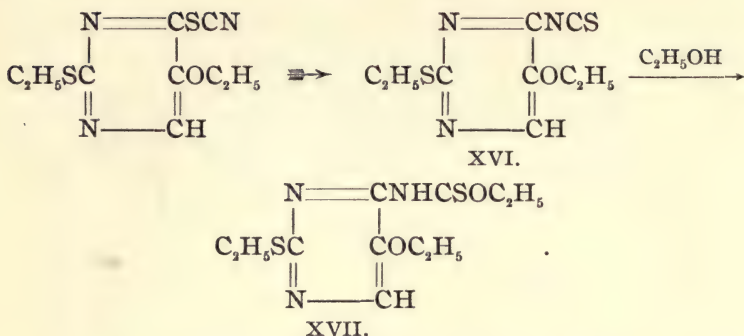
XIII.



XIV.

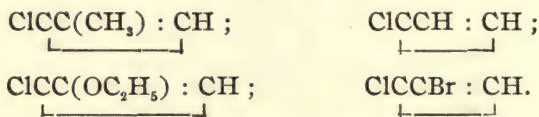


XV.



It seems very probable to the writers that the imide chlorides examined by Wheeler and Bristol¹ will give thiocyanates if treated with potassium thiocyanate under the proper conditions. Judging from the properties of 2-ethylmercapto-5-ethoxy-6-thiocyanpyrimidine, XII., their thiocyanates would be expected to undergo a rearrangement under the conditions employed in their experiments.

These four imide chlorides constitute an ideal series with which to test the rule as to whether the tendency for a thiocyanate to rearrange to an isothiocyanate is proportional to the negative character of the alkyl group. The only difference in structure is the character of the radicals occupying the 5-position. If the tendency to form isothiocyanates is directly proportional to the negative influence of these four radicals, evidently the negative character of the pyrimidines in question must be expressed by the following arrangement :



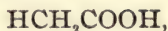
That the negative influence of the radicals occupying the 5-position is to be represented by the arrangement—CH₃, H, OC₂H₅, Br—is shown on substituting these groups in acetic acid and comparing the affinity constants² of the resulting acids.

¹ *Loc. cit.*

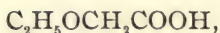
² Ostwald : *Phys. Chem.*, 3, 174-184.



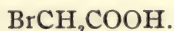
$$K = 0.00134$$



$$K = 0.0018$$



$$K = 0.0234$$

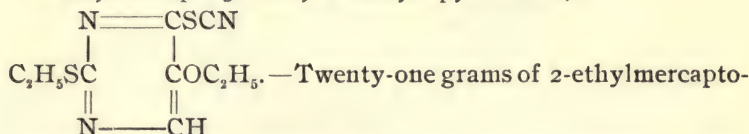


$$K = 0.138$$

The affinity constant in the case of acetic acid is decreased by the introduction of the methyl radical, while by the substitution of the more negative ethoxy group it is increased in the proportion 1 : 13. The investigation of these thiocyanate derivatives is now in progress in this laboratory.

EXPERIMENTAL PART.

2-Ethylmercapto-5-ethoxy-6-thiocyanpyrimidine,



5-ethoxy-6-chlorpyrimidine¹ and 11 grams of potassium thiocyanate were dissolved in 95 per cent alcohol and the solution boiled for 6 hours. Potassium chloride began to separate immediately on warming and by prolonged boiling the alcoholic solution assumed a red color. After the completion of the reaction the excess of alcohol was removed by evaporation and the residue treated with cold water, to extract the potassium chloride and the excess of potassium thiocyanate. We obtained a well crystallized product that was soluble in hot alcohol and benzene. It deposited from alcohol in lemon-yellow prisms, which melted, at 66°–67°, to a clear oil. When heated above its melting point it showed no signs of decomposition below 200°. It was insoluble in alkali and was not changed when warmed with aqueous ammonia. It possessed the properties of a weak base. It dissolved in strong hydrochloric acid and was reprecipitated unaltered by alkali or by dilution with water. Analysis (Kjeldahl) :

	Calculated for $\text{C}_9\text{H}_{11}\text{ON}_2\text{S}_2$.	Found.
N	17.42	17.12

¹ Johnson and McCollum : J. Biol. Chem., 1, 443 (1906).

Action of Thiobenzoic Acid and Thioacetic Acid on 2-Ethylmercapto-5-ethoxy-6-thiocyanpyrimidine.

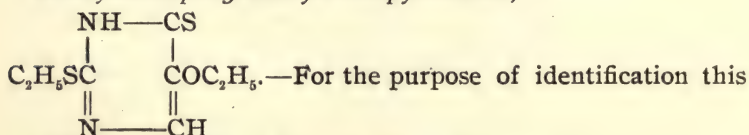
Two and five-tenths grams of the thiocyanate were dissolved in one molecular proportion of thiobenzoic acid. The substances reacted at once with the evolution of considerable heat. After warming for a few minutes in a boiling water-bath, to complete the reaction, the product was treated with a little alcohol, when it crystallized in the form of well developed, yellow prisms. It was purified for analysis by crystallization from alcohol. It melted, at 144° – 145° , to a clear oil. Nitrogen determinations agreed with the calculated value in *2-ethylmercapto-5-ethoxy-6-thiopyrimidine* (see below) :

	Calculated for $C_8H_{12}ON_2S_2$.	I.	Found. II.	III.
N	12.96	13.2	12.88	13.2

Two grams of the thiocyanate were dissolved, at the ordinary temperature, in 1 molecular proportion of thioacetic acid. After a few minutes heat began to be evolved and the mixture solidified. It was then warmed in a boiling water-bath for a few minutes. The product crystallized from 95 per cent alcohol in yellow prisms and melted, at 144° – 145° , to a clear oil. When this material was mixed with some of the compound obtained by the action of thiobenzoic acid on the thiocyanate, and heated in a capillary tube, the melting point was not lowered. The two substances were identical. We did not detect the formation of any carbon bisulphide in these reactions with thioacids.¹ When the mother liquors were treated with a solution of ferric chloride we obtained characteristic, red colored solutions, showing the presence of free thiocyanic acid. Analysis (Kjeldahl) :

	Calculated for $C_8H_{12}ON_2S_2$.	Found.
N	12.96	13.2

2-Ethylmercapto-5-ethoxy-6-thiopyrimidine,



¹ Wheeler and Merriam: J. Am. Chem. Soc., 23, 284.

compound was prepared by boiling 2-ethylmercapto-5-ethoxy-6-chlorpyrimidine with an alcoholic solution of potassium hydrosulphide. The reaction was smooth and potassium chloride precipitated at once from the alcohol. When the solution was acidified with acetic acid the pyrimidine separated as a yellow, crystalline substance. It deposited from alcohol in prisms and melted, at 144° – 145° , to a clear oil. When this material was mixed with the compounds obtained in the reactions with thioacids, described above, the melting point was not changed. Analysis :

	Calculated for $C_8H_{12}ON_3S_2$.	Found.
N	12.96	13.2

2-Ethylmercapto-5-ethoxy-6-isothiocyanpyrimidine,

$$\begin{array}{c}
 \text{N}=\text{CNCS} \\
 | \qquad \qquad | \\
 \text{C}_2\text{H}_5\text{SC} \qquad \text{COC}_2\text{H}_5. - 2\text{-Ethylmercapto-5-ethoxy-6-thiocyan-} \\
 || \qquad \qquad || \\
 \text{N} - \text{CH}
 \end{array}$$

pyrimidine shows no tendency to rearrange into the isothiocyanate at ordinary temperatures. In order to decide at what temperature this rearrangement would take place we performed the following experiments: One gram of the thiocyanate was heated in a sulphuric acid-bath, at 80° – 90° , for 1 hour. On cooling, the material crystallized immediately. It melted, at 66° – 67° , to a clear oil and was identified as the unaltered thiocyanate. It was then heated for another hour at 90° – 100° . The material solidified on cooling and melted sharply at 66° – 67° . It was then heated for 3 hours at 105° – 110° . On cooling the material refused to solidify and, after standing for several days, still retained the consistency of a syrup. That this product was an isothiocyanate was proved as follows: It reacted at once with ammonia to give practically a quantitative yield of 2-ethylmercapto-5-ethoxy-6-thioureapyrimidine (see below) which melted, at 171° – 172° , to a clear oil.

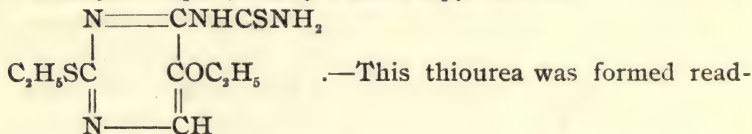
In order to obtain the isothiocyanate sufficiently pure for analysis, 10 grams of the thiocyanate were distilled under diminished pressure. Much decomposition took place, but we

obtained a fraction boiling at 228° – 235° (20–23 mm.). This oil was exceedingly hygroscopic and weighed 5 grams. When allowed to stand in a desiccator, over concentrated sulphuric acid, it finally solidified. It was exceedingly soluble in the common organic solvents and, when exposed to the air, began to assume an oily appearance. The crude material melted, at 45° – 50° , to a turbid oil. Analysis (Kjeldahl) :

	Calculated for $C_9H_{11}ON_3S_2$.	Found.
N	17.4	16.8

Two attempts were made to prepare this isothiocyanate by boiling a mixture of the chlorpyrimidine, toluene and potassium thiocyanate. In our first experiment 10 grams of the chlorpyrimidine and 5.5 grams of potassium thiocyanate were taken and the mixture boiled for 12 hours. Under these conditions we observed no evidence of any reaction. We then boiled a mixture of 5 grams of the chlorpyrimidine, 2.3 grams of potassium thiocyanate and toluene for 30 hours. On evaporating the excess of toluene and crystallizing the residue from petroleum ether, we recovered 4 grams of the unaltered chloride melting at 44° .

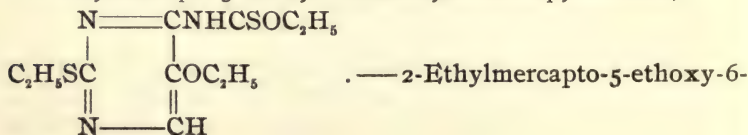
2-Ethylmercapto-5-ethoxy-6-thioureapyrimidine,



ily when the isothiocyanate above described was treated with aqueous ammonia. It deposited from hot alcohol in slender, yellow prisms, that melted at 172° , without effervescence, to a clear oil. Analysis (Kjeldahl) :

	Calculated for $C_9H_{14}ON_4S_2$.	Found.
N	21.70	21.47

2-Ethylmercapto-5-ethoxy-6-thionethylurethane pyrimidine,



thiocyanpyrimidine undergoes a rearrangement into the isomeric isothiocyanate derivative when boiled with alcohol. Thirty-five grams of 2-ethylmercapto-5-ethoxy-6-chlorpyrimidine and 20 grams of potassium thiocyanate were dissolved in 95 per cent alcohol and the solution boiled for 11 hours. When we evaporated the alcohol and treated the residue with cold water, to remove potassium chloride and potassium thiocyanate, we obtained a semi-solid which showed no signs of crystallizing after standing for 3 hours. This material was then treated with a dilute solution of sodium hydroxide. We observed that part of the substance dissolved in the alkali and the insoluble portion assumed a crystalline form. This was filtered off and recrystallized from alcohol. It deposited in prisms that melted at 66°-67°. It was identified as the thiocyanate. Analysis (Kjeldahl) :

	Calculated for $C_9H_{11}ON_3S_2$.	Found.
N	17.42	17.16

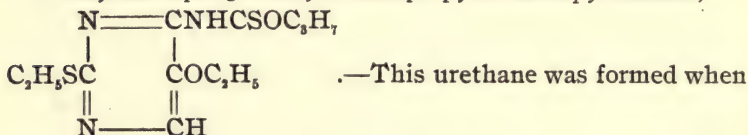
The urethane that was dissolved by the alkali was recovered when we acidified the solution with hydrochloric acid. It separated in light yellow prisms. It was insoluble in hot and cold water and very soluble in hot alcohol. It deposited from alcohol in long prisms, which showed signs of melting at 89° and then melted at 93°-94°, to an oil. The yields of thiocyanate and urethane were about equal. Analysis (Kjeldahl):

	Calculated for $C_{11}H_{17}O_2N_3S_2$.	Found.
N	14.63	14.85

In order to study the velocity of the rearrangement of the thiocyanate into its isomer in boiling ethyl alcohol, we performed the following experiments: Fifteen grams of 2-ethylmercapto-5-ethoxy-6-chlorpyrimidine and 9 grams of potassium thiocyanate were boiled in alcohol for 24 hours. After separating the urethane from the thiocyanate in the usual way and then recrystallizing the compounds from alcohol, we obtained 1.2 grams of the thiocyanate and 10 grams of the urethane. In a second experiment we used 15 grams of the chlorpyrimidine, 9 grams of potassium thiocyanate and boiled the

alcoholic solution 4 hours. We obtained 10 grams of thiocyanate or 60.6 per cent of the theoretical, and 1.3 grams of urethane. In no case did our combined yields of thiocyanate and urethane correspond to more than 60-70 per cent of the theoretical. In order to demonstrate that this loss is due to the fact that the urethane slowly volatilizes when the alcoholic solutions are evaporated, we performed the following experiment: An alcoholic solution of 15 grams of the imide chloride and 6.6 grams of potassium thiocyanate was boiled for 30 hours. The alcoholic solution was then treated with a molecular proportion of sodium ethylate, to form a sodium salt of the urethane and evaporated to dryness. We obtained 4.9 grams of thiocyanate. The urethane was obtained by neutralizing its sodium salt with acetic acid and weighed 9.85 grams. These yields accounted for 95.26 per cent of the imide chloride used in the experiment.

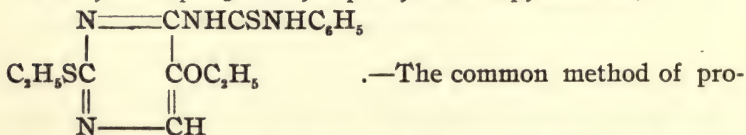
2-Ethylmercapto-5-ethoxy-6-thionpropylurethane-pyrimidine,



3 grams of 2-ethylmercapto-5-ethoxy-6-chlorpyrimidine and 2 grams of potassium thiocyanate were dissolved in normal propyl alcohol and the solution boiled for 6 hours. Under these conditions we did not obtain any thiocyanate. The urethane was purified by recrystallizing from 95 per cent alcohol. It deposited in small prisms that melted, at 56° - 57° , without effervescence, to a clear oil. Analysis (Kjeldahl):

	Calculated for $\text{C}_{12}\text{H}_{19}\text{O}_2\text{N}_3\text{S}_2$.	Found.
N	13.95	13.76

2-Ethylmercapto-5-ethoxy-6-phenylthiourea-pyrimidine,



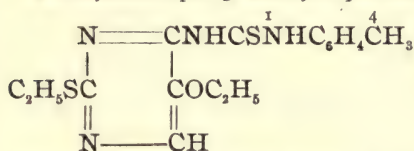
cedure in the preparation of the thioureas described in this

paper was to heat the 2-ethylmercapto-5-ethoxy-6-thiocyanpyrimidine in an oil-bath at 150°–160°, for about 30 minutes and thoroughly rearrange it to the isothiocyanate. This was then dissolved in a little benzene and combined with a molecular proportion of the organic base. The reactions were usually accompanied with evolution of heat and the yields of thioureas were practically quantitative.

The phenylthiourea derivative was soluble in hot alcohol and insoluble in water. It deposited from alcohol in distorted prisms and melted, at 82°–83°, to a clear oil. Analysis (Kjeldahl) :

	Calculated for $C_{16}H_{18}ON_4S_2$.	Found.
N	16.76	16.75

2-Ethylmercapto-5-ethoxy-6-paratolylthiourea pyrimidine,

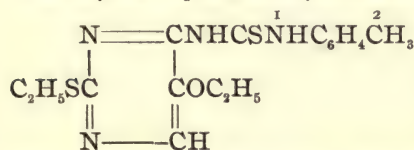


.—This thiourea was insol-

uble in water. It was soluble in hot alcohol but insoluble in cold. It deposited from alcohol in clusters of needles radiating from a common center. They melted, at 115°, to a clear oil, without effervescence. Analysis (Kjeldahl) :

	Calculated for $C_{16}H_{20}ON_4S_2$.	Found.
N	16.09	16.20

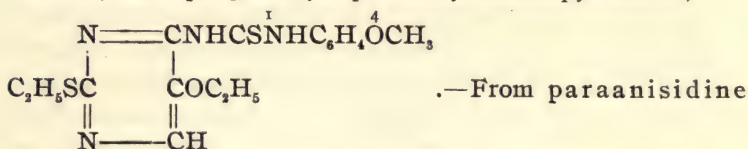
2-Ethylmercapto-5-ethoxy-6-orthotolylthiourea pyrimidine,



.—This thiourea was insol-

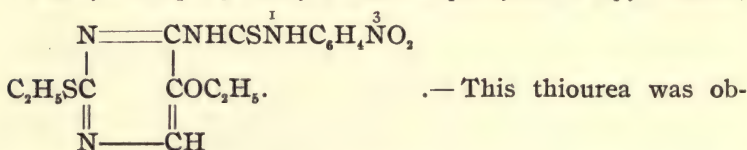
uble in water and soluble in warm alcohol. It deposited from alcohol in rhombic-shaped prisms and melted, at 129°–130°, to a clear oil.

	Calculated for $C_{16}H_{20}ON_4S_2$.	Found.
N	16.09	15.86

2-Ethylmercapto-5-ethoxy-6-paraanisylthiourea pyrimidine,

and 2-ethylmercapto-5-ethoxy-6-isothiocyanpyrimidine. This base showed little tendency to react with the isothiocyanate at ordinary temperatures. In order to complete the action the mixture was heated in a boiling water-bath, for 6 hours. The product was then washed with dilute hydrochloric acid to remove unaltered anisidine and afterwards purified by crystallizing from 95 per cent alcohol. It deposited from alcohol in rhombic prisms and melted at 122° – 123° . Analysis (Kjeldahl):

	Calculated for $\text{C}_{16}\text{H}_{20}\text{O}_2\text{N}_4\text{S}_2$.	Found.
N	15.38	15.53

2-Ethylmercapto-5-ethoxy-6-metanitrophenylthiourea pyrimidine,

tained when 1 gram of 2-ethylmercapto-5-ethoxy-6-isothiocyanate and a molecular proportion of metanitriline were dissolved in benzene and digested on the steam-bath, for 1 hour. When the benzene was evaporated the thiourea remained as an oil, which soon solidified. It was insoluble in hot water and slightly soluble in alcohol. It crystallized from benzene in the form of slender prisms which melted, at 161° , without effervescence, to a clear oil. Analysis (Kjeldahl):

	Calculated for $\text{C}_{15}\text{H}_{17}\text{O}_2\text{N}_5\text{S}_2$.	I.	Found. II.	III.	IV.
N	18.47	18.23	18.23	18.09	18.10

NEW HAVEN, CONN.,
May 5, 1906.

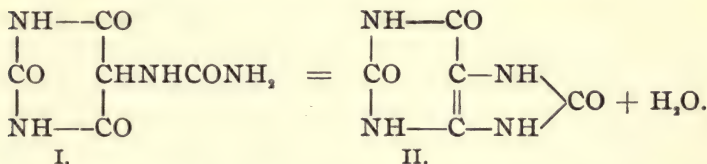
Contributions from the Sheffield Laboratory of Yale University.

CXXXII.—RESEARCHES ON PYRIMIDINES: ON THE
FORMATION OF PURINES FROM UREA-
PYRIMIDINES.

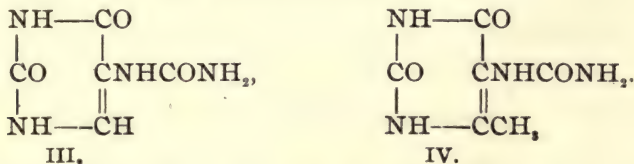
[SIXTEENTH PAPER.]

BY TREAT B. JOHNSON AND ELMER V. MCCOLLUM.

It has been shown by several investigators¹ that 5-urea-pyrimidines, in which the 4 and 6 positions are occupied by oxygen, I., condense to purines when heated with oxalic or hydrochloric acids. The condensation of 2,4,6-trioxy-5-urea-pyrimidine (pseudouric acid), I., to uric acid,² II., represents the simplest case of this method of purine formation.



On the other hand, 5-ureaprimidines, III., IV., in which hydrogen or an alkyl radical occupies the 4-position, show no tendency to undergo a similar condensation when treated with dehydrating agents. Behrend³ obtained no evidence of the formation of purines when 2,6-dioxy-5-ureaprimidine (hydroxyxanthine), III., and 2,6-dioxy-4-methyl-5-ureaprimidine (methylhydroxyxanthine), IV., were treated, under various conditions, with phosphorus pentachloride, sulphuric acid, acetic anhydride and chlorosulphonic acid.

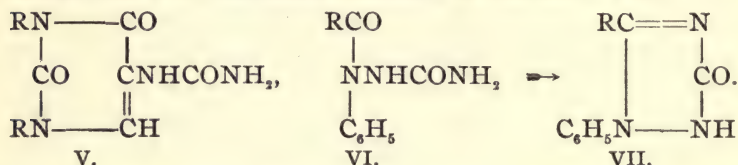


¹ Fischer and Ach: Ber. d. chem. Ges., 28, 2473. Fischer: *Ibid.*, 30, 559; 33, 1701. Sembritski: *Ibid.*, 30, 1814. Armstrong: *Ibid.*, 33, 2308.

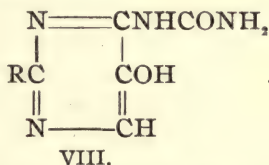
² Fischer and Ach: *Loc. cit.*

³ Ann. Chem. (Liebig), 229, 40; 231, 248, 251; 240, 1.

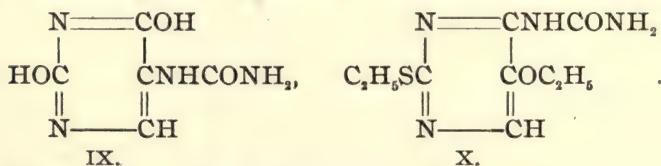
This observation of Behrend's was later confirmed by Widman.¹ He investigated the behavior of 2,6-dioxy-5-ureapyrimidines, V., towards potassium hydroxide. On account of the structural relationship between such ureapyrimidines and acylsemicarbazides, VI., it was important to compare their behavior towards this reagent. He found that the ureapyrimidines, V., could be recovered unaltered after warming with dilute solutions of potassium hydroxide, while the acylsemicarbazides, VI., condensed smoothly to triazoles,² VII.



On account of the pronounced difference in behavior of 4,6-dioxy-5-ureapyrimidines from 6-oxy-5-ureapyrimidines, III. and IV., it seemed desirable to prepare a 5-hydroxy-6-ureapyrimidine, VIII. It was of interest to decide whether such a ureapyrimidine derivative would undergo an inner condensation to form a purine.



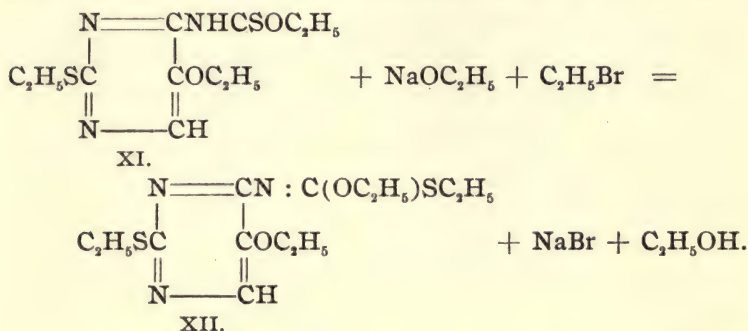
We have selected as a suitable representative of this new class of hydroxyureapyrimidines 2-ethylmercapto-5-ethoxy-6-ureapyrimidine, X. The structural relationship between this pyrimidine and Behrend's hydroxyxanthine, III., is illustrated by representing the oxygen derivative in its *enol* form, IX. :



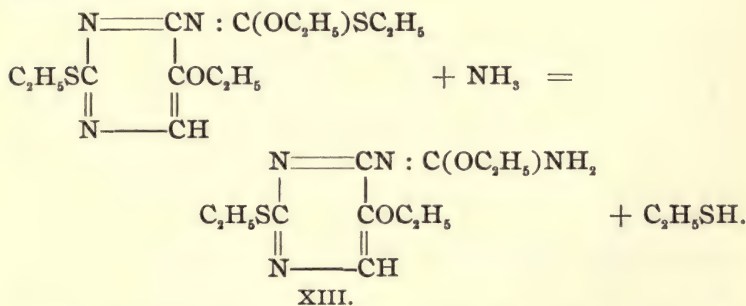
¹ Ber. d. chem. Ges., 29, 1954 (1896).

² Widman: Ber. d. chem. Ges., 29, 1946.

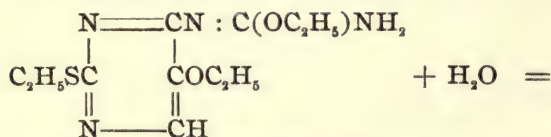
We have prepared this urea derivative, X., in the following manner : When 2-ethylmercapto-5-ethoxy-6-thionethylurethanepyrimidine,¹ XI., was treated with molecular proportions of sodium ethylate and ethyl bromide, it gave 2-ethylmercapto-5-ethoxy-6-iminothioethylcarbonatepyrimidine, XII. :



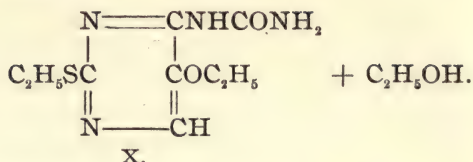
This iminothiocarbonate, XII., evolved ethylmercaptan when treated with alcoholic ammonia and was converted, practically quantitatively, into 2-ethylmercapto-5-ethoxy-6-pseudoethylureaepyrimidine, XIII. :



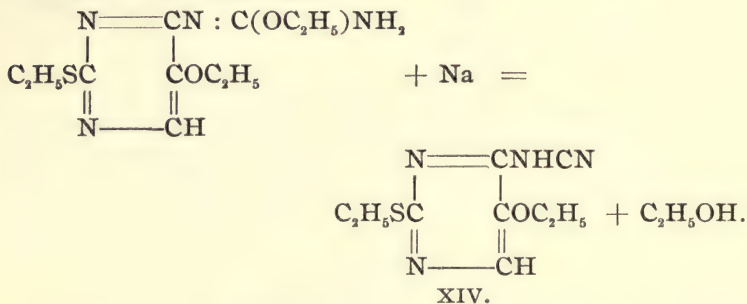
This pseudourea, XIII., then gave the normal urea, X., when treated with cold, concentrated hydrochloric acid :



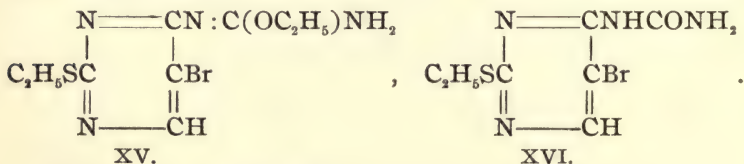
¹ Johnson and McCollum : THIS JOURNAL, 36, 136 (1906).



Attempts to condense the pseudourea, XIII., or the normal urea, X., to purine derivatives were without success. Sodium, in boiling benzene, attacked the pseudoureapyrimidine, XIII., to form a cyanaminopyrimidine, XIV. When the normal ureapyrimidine, X., was treated in the same manner it was recovered unaltered. It underwent decomposition when heated above its melting point :

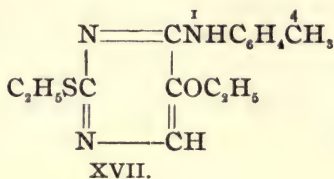


The 5-ethoxy radical in the above ureapyrimidines, XIII., and X., apparently is as firmly linked as the bromine atoms in the 5-brom-6-ureapyrimidines that were examined by Wheeler and Bristol.¹ They were unable to condense 2-ethylmercapto-5-brom-6-pseudoethylureapyrimidine, XV., or 2-ethylmercapto-5-brom-6-ureapyrimidine, XVI., to purine derivatives. The bromine atom in these compounds could not be removed by heating with pyridine, or by digesting in benzene with metallic sodium :



¹ THIS JOURNAL, 33, 448 (1905).

In this paper we also describe a series of substituted 6-aminopyrimidines that we have prepared by warming 2-ethylmercapto-5-ethoxy-6-chlorpyrimidine¹ with organic bases. These derivatives are characterized by their stability towards boiling acids. 2-Ethylmercapto-5-ethoxy-6-paratoluidinopyrimidine, XVII., could be boiled with concentrated hydrochloric acid without removing the mercapto radical.



EXPERIMENTAL.

Diethylformylglycollate, $\text{C}_2\text{H}_5\text{OCH}(\text{CHO})\text{COOC}_2\text{H}_5$. — The sodium salt of this ester was described in a previous paper by Johnson and McCollum.² We now find that the free ester can easily be prepared from this sodium salt. It separated as a colorless oil when an aqueous solution of the sodium salt was acidified with hydrochloric acid. It was purified by fractional distillation, under diminished pressure. A fraction that distilled at $115^\circ\text{--}118^\circ$ (35 mm.) was used for the analytical determinations.

I. 0.4711 gram substance gave 0.8763 gram CO_2 and 0.3190 gram H_2O .

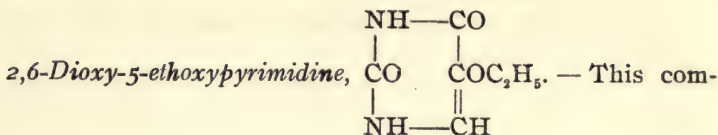
II. 0.4732 gram substance gave 0.8853 gram CO_2 and 0.3176 gram H_2O .

III. 0.4677 gram substance gave 0.8762 gram CO_2 and 0.3121 gram H_2O .

	Calculated for $\text{C}_7\text{H}_{12}\text{O}_4$.	I.	Found. II.	III.
C	52.5	50.72	51.02	51.09
H	7.5	7.33	7.45	7.41

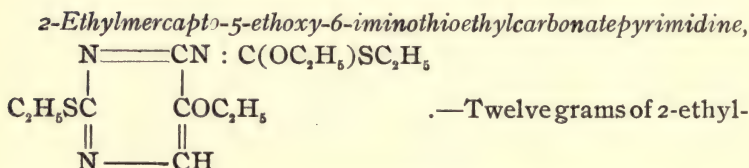
¹ Johnson and McCollum: *Loc. cit.*

² J. Biolog. Chem., 1, 437.



pound was described in a previous publication by Johnson and McCollum.¹ It was obtained, associated with isobarbituric acid, when 2-ethylmercapto-5-ethoxypyrimidine was heated in a sealed tube, with hydrochloric acid. We find that this pyrimidine can easily be prepared by boiling 2-methylmercapto-5-ethoxypyrimidine² with hydrochloric acid. It agreed in its properties with the compound described in our former paper. Analysis (Kjeldahl) :

	Calculated for $\text{C}_6\text{H}_8\text{O}_3\text{N}_2$.	Found.
N	17.95	18.00



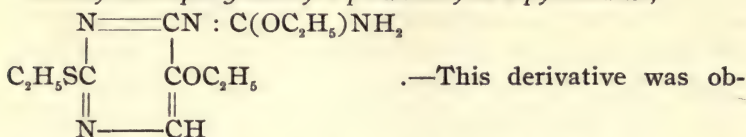
mercapto-5-ethoxy-6-thionethylurethanepyrimidine² were dissolved in alcohol containing one molecular proportion of metallic sodium. Four and five-tenths grams of ethyl bromide were then added and the solution allowed to stand at the ordinary temperature until neutral to litmus. After the reaction was complete the excess of alcohol was evaporated on the steam-bath, and the oily residue treated with cold water to remove sodium bromide. An oil was obtained which was extracted with ether and dried over calcium chloride. When the ether was evaporated, the diethylcarbonate remained as an oil which would not solidify. Analysis (Kjeldahl) :

	Calculated for $\text{C}_{18}\text{H}_{21}\text{O}_2\text{N}_3\text{S}_2$.	Found.
N	13.33	12.94

¹ *Loc. cit.*

² Johnson and McCollum : *Loc. cit.*

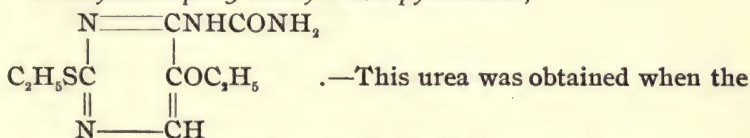
2-Ethylmercapto-5-ethoxy-6-pseudoethylureapyrimidine,



tained when dry ammonia gas was passed into an alcoholic solution of the above iminothioethylcarbonate. When the alcoholic solution was evaporated to dryness the pseudourea was obtained as a well crystallized compound. It was very soluble in alcohol and benzene and was purified for analysis by recrystallizing from ligroin. It melted, at 77° , to a clear oil. Analysis (Kjeldahl) :

	Calculated for $\text{C}_{11}\text{H}_{18}\text{O}_2\text{N}_4\text{S}$.	Found.
N	20.74	20.40

2-Ethylmercapto-5-ethoxy-6-ureapyrimidine,



above pseudourea was allowed to stand dissolved in concentrated hydrochloric acid. After remaining a few days, the urea was precipitated by adding water. It was readily soluble in hot alcohol and deposited from cold alcohol in prismatic crystals, which melted at $166^\circ\text{--}167^\circ$, with slight effervescence, to a clear oil. It gave a strong test for sulphur, but did not contain chlorine. When mixed with 2-ethylmercapto-5-ethoxy-6-oxyprymidine¹ (m. p. $166^\circ\text{--}167^\circ$) the melting point was lowered to $140^\circ\text{--}143^\circ$. Analysis (Kjeldahl) :

	Calculated for $\text{C}_9\text{H}_{14}\text{O}_2\text{N}_4\text{S}$.	Found.
N	23.14	23.17

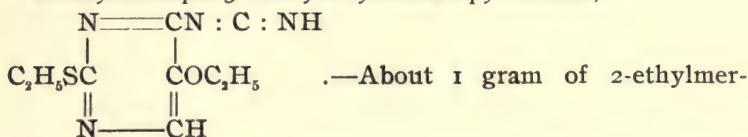
One gram of this urea and 1.5 grams of metallic sodium were suspended in benzene and the mixture boiled for 20 hours. There was no evidence of any reaction except that the sodium

¹ Johnson and McCollum : *Loc. cit.*

became coated with a thin deposit. When the benzene was evaporated and the sodium dissolved in alcohol, we obtained a crystalline deposit that melted at about 166° . It crystallized from hot, 95 per cent alcohol in prisms that melted at 166° – 167° , with slight effervescence. It was identified as the unaltered urea. We did not observe the formation of the cyanaminopyrimidine (see below). Analysis (Kjeldahl) :

	Calculated for $C_9H_{14}O_2N_4S$.	Found.
N	23.14	23.07

2-Ethylmercapto-5-ethoxy-6-cyanaminopyrimidine,

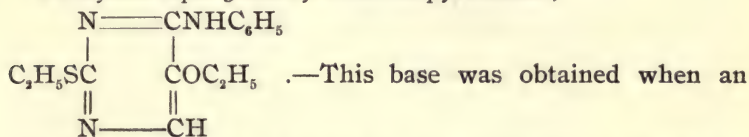


capto-5-ethoxy-6-pseudoethylureapyrimidine was dissolved in dry benzene and treated with a slight excess over one molecular proportion of metallic sodium. The mixture was then boiled for 40 hours. The sodium underwent a complete change by this treatment and was transformed into a slimy precipitate. On filtering and evaporating the benzene there was no residue. The precipitate that remained on the filter was dissolved in alcohol and the solution evaporated to dryness. The residue was then dissolved in cold water. When this solution was acidified with acetic acid a white, crystalline product separated in the form of prisms. The substance melted sharply at 167° – 168° , with only slight effervescence. It was soluble in alkali and was reprecipitated by acids. It was insoluble in cold, but readily soluble in hot water and alcohol. When dissolved in boiling water it slowly decomposed. On cooling it deposited in prismatic crystals that melted at about 165° – 166° . When the cyanamide derivative (m. p. 167° – 168°) was mixed with the above urea (m. p. 166° – 167°) the melting point was lowered to 148° – 155° . Analysis (Kjeldahl) :

	Calculated for $C_9H_{12}ON_4S$.	Found.
N	25.00	24.95

About 0.5 gram of the cyanamide derivative was allowed to stand dissolved in a few cc. of concentrated hydrochloric acid. A deposit of slender prisms was obtained which gave a strong test for chlorine. They melted at 175° – 180° , with violent effervescence, and had all the properties of a hydrochloric acid salt. On treating with dilute ammonia they completely dissolved, but on standing the solution deposited prismatic crystals that melted at 166° – 167° . This was identified as 2-ethylmercapto-5-ethoxy-6-ureapyrimidine. When it was mixed with this urea the melting point was not lowered.

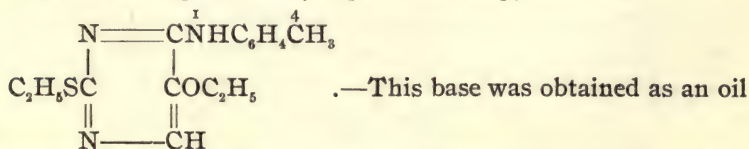
2-Ethylmercapto-5-ethoxy-6-ani.inopyrimidine,



alcoholic solution of 3 grams of 2-ethylmercapto-5-ethoxy-6-chlorpyrimidine and 2.8 grams of aniline were boiled for 24 hours. It was insoluble in water and very soluble in alcohol. It deposited from ligroin in large prisms, which melted at 60° . Analysis (Kjeldahl) :

	Calculated for $\text{C}_{14}\text{H}_{17}\text{ON}_3\text{S}$.	Found.
N	15.27	15.19

2-Ethylmercapto-5-ethoxy-6-paratoluidinopyrimidine,



when an alcoholic solution of 2-ethylmercapto-5-ethoxy-6-chlorpyrimidine and the calculated quantity of paratoluidine was boiled for 10 hours. It formed a well crystallized hydrochloride, that deposited from water in hair-like crystals and melted at 105° – 106° , with effervescence. Analysis (Kjeldahl):

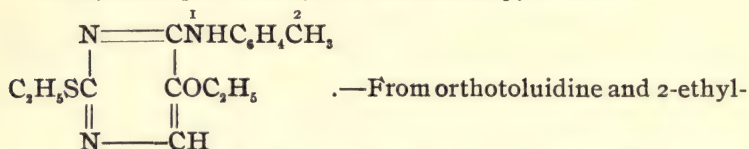
	Calculated for $\text{C}_{16}\text{H}_{19}\text{ON}_3\text{S} \cdot \text{HCl}$.	Found.
N	12.90	12.71

When the hydrochloride was treated with dilute ammonia the free base precipitated as an oil. It was soluble in ether and ligroin. It deposited from ligroin in long prisms, that melted at 72° . Analysis (Kjeldahl) :

	Calculated for $C_{15}H_{19}ON_3S$.	Found.
N	14.53	14.57

This mercaptopyrimidine can be boiled with concentrated hydrochloric acid without decomposition. After boiling 0.7 gram with an excess of hydrochloric acid, for 12 hours, it was recovered unaltered and melted sharply at 72° .

2-Ethylmercapto-5-ethoxy-6-orthotoluidinopyrimidine,



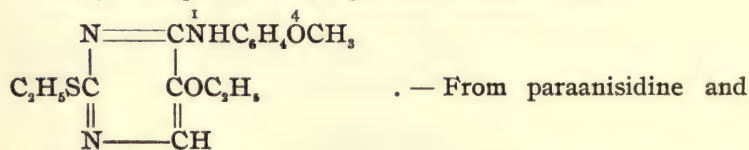
mercapto-5-ethoxy-6-chlorpyrimidine. Its hydrochloric acid salt crystallized from alcohol in prisms, that decomposed at 140° – 145° . The salt is not stable in aqueous solution and dissociates into the base and hydrochloric acid. Analysis (Kjeldahl):

	Calculated for $C_{15}H_{19}ON_3S.HCl$.	Found.
N	12.90	12.30

The free base is insoluble in water, and very soluble in alcohol. It deposited from alcohol in flat prisms, that melted at 80° . It was insoluble in ligroin. Analysis (Kjeldahl) :

	Calculated for $C_{15}H_{19}ON_3S$.	Found.
N	14.53	14.49

2-Ethylmercapto-5-ethoxy-6-paraanisidinopyrimidine,



2-ethylmercapto-5-ethoxy-6-chlorpyrimidine. This reaction

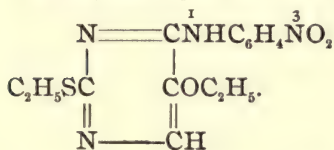
was not as smooth as those with the preceding amines. The base was first obtained as an oil which would not solidify. It was dissolved in dry benzene and the solution saturated with dry hydrochloric acid gas. The hydrochloride deposited in prismatic crystals. It was purified by recrystallization from acetone or ethyl acetate and was insoluble in benzene and ligroin. Analysis (Kjeldahl) :

	Calculated for $C_{15}H_{19}O_2N_3S.HCl$.	Found.
N	12.29	12.19

When the hydrochloride was treated with ammonia the base was obtained as an oil which finally solidified. It deposited from alcohol in stout prisms, that melted at 68° – 69° , without effervescence, to a clear oil. It was insoluble in water. Analysis (Kjeldahl) :

	Calculated for $C_{15}H_{19}O_2N_3S$.	I.	Found.	II.
N	13.77	13.77		13.81

2-Ethylmercapto-5-ethoxy-6-metanitroanilinopyrimidine,



.—The hydrochloride of this

pyrimidine base crystallized from alcohol and melted at 125° – 135° , with effervescence. The base was insoluble in water. It deposited from alcohol in long needles, which melted, at 125° , to a clear oil. Analysis (Kjeldahl) :

	Calculated for $C_{14}H_{16}O_3N_4S$.	Found.
N	17.50	17.13

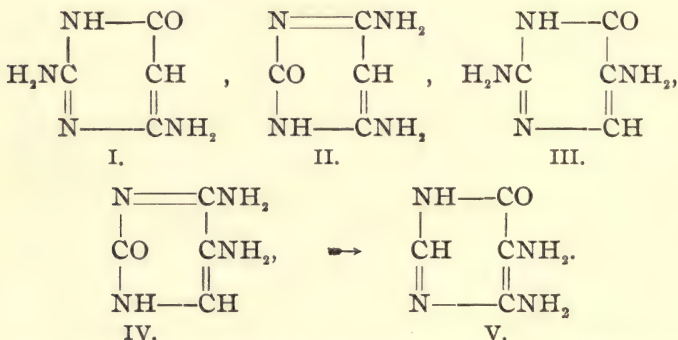
Contributions from the Sheffield Laboratory of Yale University.

CXXXIII. — RESEARCHES ON PYRIMIDINES: ON
5-NITROCYTOSINE AND ITS REDUCTION
TO 2-OXY-5,6-DIAMINOPYRIMIDINE.

[SEVENTEENTH PAPER.]

BY TREAT B. JOHNSON, CARL O. JOHNS AND FREDERICK W. HEYL.

There are five possible monooxydiaminopyrimidines in which the oxygen atom can occupy positions 2 and 6, assuming that the amino groups are attached to carbon. Their formulae are given below, I.-V. Three of these have been synthesized, *viz.* : 2,4-diamino-6-oxypyrimidine,¹ I., 2-oxy-4,6-diaminopyrimidine,² II., and 6-oxy-2,5-diaminopyrimidine,³ III. In this paper we shall describe the fourth member of this series — 2-oxy-5,6-diaminopyrimidine, IV. :



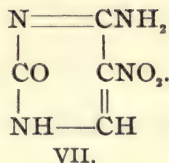
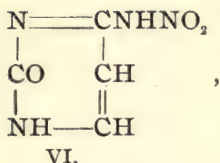
In a previous paper from this laboratory, Wheeler and Johnson⁴ have shown that cytosine is converted into nitrocytosine when treated with a mixture of nitric and sulphuric acids. No attempt was made to establish the structure of this nitro derivative. They assumed, nevertheless, on account of the unstable character of the products formed on reduction, that they were dealing with a nitramine, VI., instead of 5-nitrocytosine, VII. :

¹ Traube : Ber. d. chem. Ges., **33**, 1371.

² Wheeler and Jamieson : THIS JOURNAL, **32**, 342 (1904).

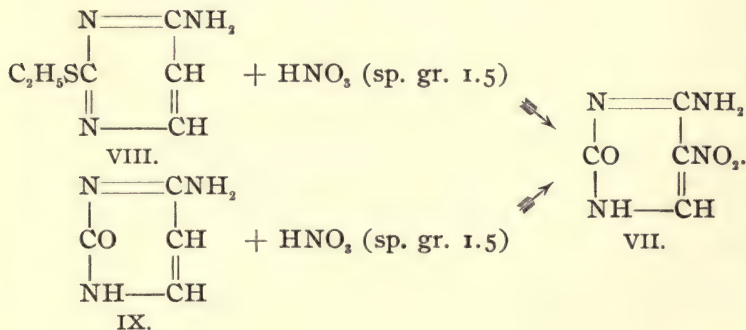
³ Johnson and Johns : *Ibid.*, **34**, 554 (1905).

⁴ *Ibid.*, **31**, 591 (1904).



In the course of our work on oxydiaminopyrimidines it was necessary to decide whether the structure of nitrocytosine is to be represented by Formula, VI., or by Formula VII. If it is a 5-nitropyrimidine, VII., it seemed probable that it might give a diaminopyrimidine when reduced under the proper conditions.

The nitrocytosine that was used in this research was prepared by dissolving 2-ethylmercapto-6-aminopyrimidine,¹ VIII., in a mixture of concentrated nitric and sulphuric acids. It was converted, practically quantitatively, into the same nitropyrimidine, VII., as was obtained from cytosine,² IX.

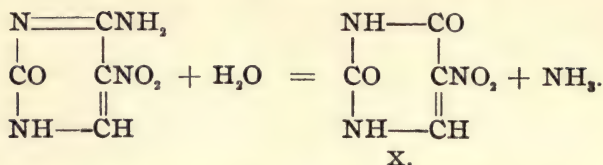


We now conclude that this nitro derivative is 2-oxy-5-nitro-6-aminopyrimidine, VII., and not a nitramine, VI., as represented in the previous paper.² That this conclusion is correct is established by the following data :

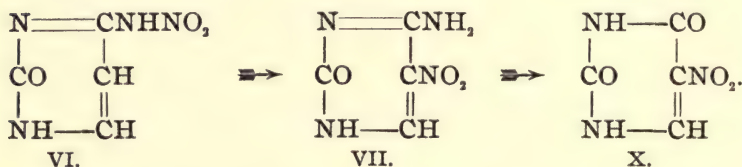
When nitrocytosine was heated under pressure, with 20 per cent sulphuric acid, it was converted into nitrouracil, X. :

¹ Wheeler and Johnson : THIS JOURNAL, 29, 497 (1903).

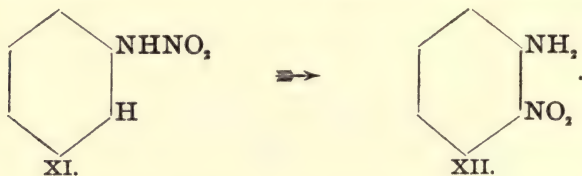
² Wheeler and Johnson : *Loc. cit.*



This result is analogous to those obtained when cytosine and 5-methylcytosine¹ were heated with sulphuric acid. They were converted into uracil and thymine, respectively. While this result supports the assumption that the nitro group in nitrocytosine occupies the 5-position, yet there was the possibility of the nitramine, VI., giving nitrouracil under the same conditions. This would involve a rearrangement of the nitro group from the amino radical to the 5-position in the pyrimidine ring, and then a hydrolysis to nitrouracil, as represented above :



Analogous rearrangements have been observed to take place in the benzene series. Bamberger² found, for example, that phenylnitramine, XI., was rearranged into orthonitroaniline, XII., when warmed with sulphuric or hydrochloric acids :



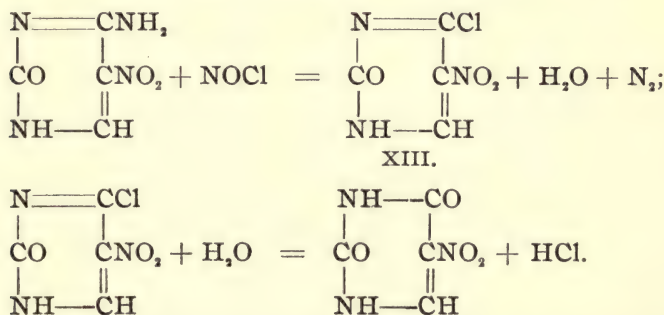
Although this rearrangement is theoretically possible, yet it did not seem probable to the writers because nitrocytosine is prepared under conditions that are not favorable for the forma-

¹ Wheeler and Johnson : *Loc. cit.*

² Ber. d. Chem. Ges. 26, 490.

tion of a nitramine. Furthermore, we have obtained experimental evidence which shows that this rearrangement does not take place.

It has been observed by several investigators¹ that the amino radical in amino acids is replaced by chlorine and bromine when these acids are treated with nitrosyl chloride and nitrosyl bromide. We have investigated the behavior of nitrosyl chloride towards nitrocytosine and find that this pyrimidine is converted smoothly into nitrouracil when warmed with an aqueous solution of the reagent.² This reaction involves the intermediate formation of 2-oxy-5-nitro-6-chlorpyrimidine, XIII. Under the conditions employed in our experiment this imide chloride, XIII., would be decomposed with the production of nitrouracil and hydrochloric acid, as follows :



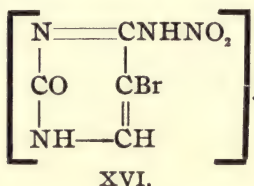
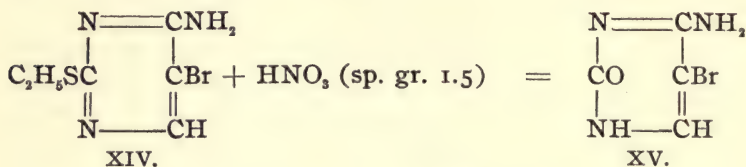
It appears to the writers that this method of formation of nitrouracil from nitrocytosine excludes the possibility of a rearrangement of the nitro group. The conditions of the reaction are far less favorable for a rearrangement than those employed in the preparation of nitrocytosine from 2-ethylmercapto-6-aminopyrimidine.

Furthermore, the following result would seem to indicate that there is no tendency for 2-mercapto-6-aminopyrimidines to form nitramines even when it is impossible for a nitro group to enter the 5-position in the pyrimidine ring. When 2-ethyl-

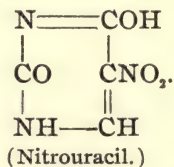
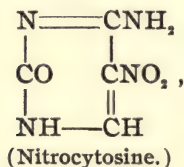
¹ Tilden and Forster : J. Chem. Soc., 67, 489. Tilden and Marshall : *Ibid.*, 67, 494. Walden : Ber. d. chem. Ges., 29, 134. Fischer : Ann. Chem. (Liebig), 340, 171. Stanek : Z. physiol. Chem., 46, 263 (1905).

² Stanek : *Loc. cit.*

mercapto-5-brom-6-aminopyrimidine,¹ XIV., was dissolved in a mixture of nitric and sulphuric acids it was converted, smoothly, into 5-bromcytosine,² XV. We obtained no evidence of the formation of a nitramine, XVI.



It has been the usual experience, when a pyrimidine having a hydrogen atom in the 5-position is attacked by bromine, that this hydrogen is easily replaced by the halogen.³ We now find that bromine has no action on nitrocytosine. This result is in accord with previous observations and again indicates that the nitro group occupies the 5-position in this pyrimidine. Behrend⁴ observed that nitrouracil was recovered unaltered after heating with liquid bromine, at 100° :



The above data and the facts that nitrocytosine does not

¹ Wheeler and Johnson : THIS JOURNAL, **31**, 604.

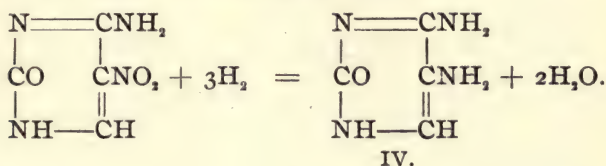
² Wheeler and Johnson : *Loc. cit.*

³ Wheeler and Johnson : THIS JOURNAL, **29**, 504. *Ibid.*, **31**, 603. Gabriel and Colman : Ber. d. chem. Ges., **34**, 1238. Wheeler and Bristol : THIS JOURNAL, **33**, 437. Johnson and Johns : *Ibid.*, **34**, 175. J. Biolog. Chem., **1**, 305.

⁴ Ann. Chem. (Liebig), **240**, 11.

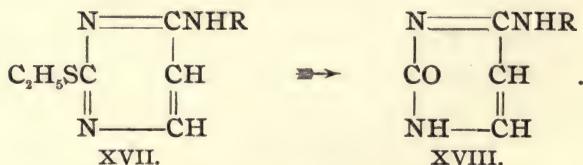
give "Liebermann's reaction,"¹ or Thiele and Lachman's² "nitramine reaction," prove that nitrocytosine is a 2-oxy-5-nitro-6-aminopyrimidine, as represented by Formula VII.

We find that 5-nitrocytosine can be reduced with aluminium-amalgam to 2-oxy-5,6-diaminopyrimidine, IV. :



The reduction was very smooth, but we encountered several experimental difficulties before we succeeded in isolating the product. The base is especially characterized by the ease with which it undergoes decomposition in aqueous solution. It is the most unstable aminopyrimidine that we have prepared in this laboratory. It gave a very insoluble picrate and was precipitated from its aqueous solution by potassiobismuth iodide, mercuric chloride and phosphotungstic acid. Like 2,5-diamino-6-oxy-pyrimidine,³ it contained 1 molecule of water of crystallization.

In this paper we also describe a series of substituted 2-ethylmercapto-6-aminopyrimidines, XVII., that we have prepared by heating 2-ethylmercapto-6-chloropyrimidine⁴ with aromatic bases. These mercaptopyrimidines were converted into cytosine derivatives, XVIII., when boiled with mineral acids :



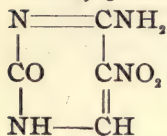
¹ Ber. d. chem. Ges., **7**, 248. Baeyer: *Ibid.*, **7**, 966. Mahla and Tiemann: *Ibid.*, **29**, 2810. Francesconi and Angelucci: Gazz. chim. ital., **31**, II., 302 (1901). Scholl: Ann. Chem. (Liebig), **338**, 3 (1904).

² Ann. Chem. (Liebig), **288**, 269 (1895).

³ Johnson and Johns: *Loc. cit.*

⁴ Wheeler and Johnson: *Loc. cit.*

EXPERIMENTAL, PART.

2-Oxy-5-nitro-6-aminopyrimidine (5-Nitrocytosine),

—This compound has been described in a previous paper.¹ It was obtained by nitrating cytosine in the presence of sulphuric acid. We find that it can be obtained very easily by nitrating 2-ethylmercapto-6-aminopyrimidine.² The largest yield of nitrocytosine was obtained when we proceeded under the following conditions: Nineteen cc. of concentrated sulphuric acid were mixed with 37 cc. of nitric acid (sp. gr. 1.5). To this mixture were then slowly added 12.5 grams of the mercaptopyrimidine. The reaction was very violent and the pyrimidine dissolved immediately with evolution of much heat. After all the pyrimidine had been added the solution was allowed to stand at the ordinary temperature for about 15–16 hours. The mixture was then poured upon crushed ice and the acids neutralized with concentrated ammonia. The nitropyrimidine deposited from the neutral solution as a white, microscopic powder. It was purified by recrystallization from hot water. We obtained 10.5 grams of the nitropyrimidine, corresponding to 83.5 per cent of the theoretical yield. Analysis (Kjeldahl):

	Calculated for $\text{C}_4\text{H}_4\text{O}_3\text{N}_4$.	Found.
N	35.89	35.72

The Hydrochloride of 5-Nitrocytosine.—Nitrocytosine was dissolved in warm, dilute hydrochloric acid. Upon cooling, the hydrochloride deposited in clusters of needle-like prisms. They did not decompose below 300°. Analysis (Kjeldahl):

	Calculated for $\text{C}_4\text{H}_4\text{O}_3\text{N}_4 \cdot \text{HCl}$.	Found.
N	29.09	29.2

Behavior of 5-Nitrocytosine when Heated with Sulphuric Acid under Pressure.—Two grams of 5-nitrocytosine were heated in

¹ Wheeler and Johnson: *Loc. cit.*

² Wheeler and Merriam: *Loc. cit.*

a sealed tube, with 20 per cent sulphuric acid, for 3 hours, at 185° – 197° . When the tube was examined there was no pressure and slender prisms had deposited in the acid solution. They decomposed, with effervescence, at about 275° – 277° . The compound was insoluble in acids and soluble in ammonia and in sodium hydroxide. It gave no test for sulphuric acid when warmed with a solution of barium chloride, and agreed in its behavior with that of nitrouracil. In order to demonstrate that it was nitrouracil the material was reduced in an ammoniacal solution with aluminium amalgam. After filtering from aluminium hydroxide and concentrating the filtrate to a small volume, aminouracil deposited in needles. When a solution of the base was treated with picric acid we obtained the characteristic picrate of aminouracil. It sintered at 147° and then melted at 247° , with effervescence. Analysis of the free base:

	Calculated for $C_4H_5O_2N_3$.	Found.
N	33.06	32.9

Behavior of 5-Nitrocytosine when Heated with a Hydrochloric Acid Solution of Nitrosyl Chloride.—A solution of nitrosyl chloride was prepared according to the directions given by Stanek.¹ Three grams of nitrocytosine were heated in a sealed tube, with 40 cc. of the nitrosyl chloride solution, for 4 hours, at 85° – 95° . It was then allowed to stand at the ordinary temperature for 3 days. A clear solution resulted, which slowly evolved nitrogen. When the tube was opened there was considerable pressure and a crystalline precipitate was suspended in the solution. This was difficultly soluble in hot water. It deposited, on cooling, in clusters of radiating prisms. They had no definite melting point but decomposed, without melting, when heated above 250° . It was insoluble in acids, soluble in alkalis and did not respond to a test for chlorine. A nitrogen determination agreed with the calculated value in nitrouracil (Kjeldahl):

	Calculated for $C_4H_5O_4N_3$.	Found.
N	26.75	27.00

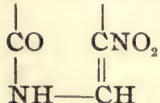
¹ Z. physiol. Chem., 46, 265.

Action of Nitric Acid on 2-Ethylmercapto-5-brom-6-aminopyrimidine.—This mercaptobrompyrimidine¹ was nitrated under practically the same conditions as were employed in the preparation of 5-nitrocytosine from 2-ethylmercapto-6-aminopyrimidine. Eight cc. of nitric acid (sp. gr. 1.5) were mixed with 4 cc. of concentrated sulphuric acid. Two and five-tenths grams of the mercaptopyrimidine were then slowly added to this acid mixture. Much heat was evolved and the mercaptopyrimidine dissolved at once, but the reaction was not as violent as in the nitration of 2-ethylmercapto-6-aminopyrimidine. After standing for 12 hours the solution was poured upon crushed ice and the acids neutralized with ammonia. When the liquid was concentrated to a volume of 25 cc. and cooled, a microscopic powder deposited. The material was purified by crystallization from hot water. It decomposed, without melting, when heated above 230°. It contained bromine but did not respond to a test for sulphur. A nitrogen determination agreed with the calculated value in 5-bromcytosine (Kjeldahl) :

	Calculated for $C_4H_4ON_3Br$.	Found.
N	22.10	22.17

Action of Bromine on 5-Nitrocytosine.—This pyrimidine was not attacked by bromine. It was suspended in glacial acetic acid and treated with a large excess of bromine. There was no apparent change after standing for 2 days. More bromine was then added to the acetic acid and the solution warmed in a water-bath. Under these conditions no hydrobromic acid was evolved and the nitrocytosine was recovered unaltered.

2-Oxy-5-nitro-6-phenylureaprimidine,



.—Molecular proportions of finely

pulverized 5-nitrocytosine and phenylisocyanate were heated together, at 100°, for several hours. The reaction was, apparently, perfectly smooth. When it was complete the urea

¹ Wheeler and Johnson : *Loc. cit.*

was washed with alcohol, to remove any unaltered phenylisocyanate and then with cold, 20 per cent hydrochloric acid, to remove unaltered nitrocytosine. It was then thoroughly washed with water and dried at 100°. It was practically insoluble in all solvents and slowly decomposed, without melting, when heated above 215°. Analysis (Kjeldahl) :

	Calculated for $C_{11}H_9O_4N_5$.	Found.
N	25.45	25.9

Action of Acetic Anhydride on Nitrocytosine.—5-Nitrocytosine does not react in a smooth manner with acetic anhydride. When boiled with the anhydride it slowly dissolves to a yellow solution that assumes a red color on prolonged boiling. Different products are formed by this treatment and in varying proportions, depending upon the quantity of anhydride used and on the length of time of boiling. In every experiment that we performed we invariably obtained mixtures of a monoacetyl and a diacetyl derivative, with unaltered material. It was extremely difficult to obtain conditions favorable for the formation of a single acetyl compound.

In one experiment 0.5 gram of nitrocytosine was dissolved in 8 cc. of boiling acetic anhydride. The solution was then immediately cooled, when we obtained a deposit of lenticular shaped crystals. They were soluble in hot water and deposited, on cooling, in prisms. When crystallized a second time the material deposited in fern-like forms that began to darken at 205° and decomposed at about 260°, without effervescence. Analysis (Kjeldahl) :

	Calculated for $C_6H_6O_4N_4$.	Found.
N	28.28	28.35

In two other experiments we duplicated the above conditions, except that we boiled the anhydride solution for a longer time. We obtained material that deposited from water in prismatic crystals. While the crystalline form suggested purity, the melting points were unsatisfactory and the nitrogen determinations indicated that we were dealing with a mixture of about equal proportions of a monoacetyl and a diacetyl

derivative. The material that was analyzed decomposed at 206° – 208° , with effervescence.

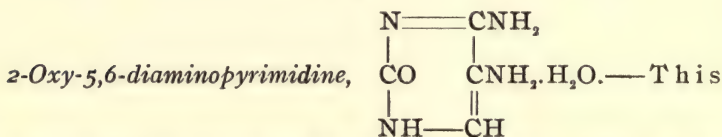
N	Calculated for		Average.	Found.	
	$C_6H_6O_4N_4$.	$C_8H_8O_6N_4$.		I.	II.
	28.28	23.33	25.8	26.0	25.81

In another experiment we used freshly distilled acetic anhydride. One and seven-tenths grams of the nitropyrimidine were suspended in 10 cc. of the anhydride and the mixture boiled until the pyrimidine completely dissolved. Upon cooling, 1.3 grams of material deposited. It was difficultly soluble in hot water and deposited, on cooling, in needle-like prisms that decomposed at 273° – 275° , with violent effervescence. A nitrogen determination agreed with the calculated value for a diacetyl derivative :

N	Calculated for	Found.
	$C_8H_8O_6N_4$.	
	23.33	23.23

The original anhydride filtrate was allowed to evaporate to dryness. We obtained a crystalline residue that proved to be a mixture. After several recrystallizations from water we finally isolated a product that possessed all the properties of the original 5-nitrocytosine. Analysis (Kjeldahl) :

N	Calculated for	Found.
	$C_4H_4O_3N_4$.	
	35.89	35.3



pyrimidine was formed by reducing 5-nitrocytosine with aluminium amalgam. We had great difficulty in preparing this base and it was only after obtaining negative results from several experiments that we eventually found conditions under which it was possible to isolate it. We finally succeeded in making the compound in the following manner: Three grams of finely pulverized 5-nitrocytosine were suspended in cold water, in contact with aluminium amalgam. The temperature of the solution was not allowed to rise above 35° during the reduction, and the

mixture was thoroughly agitated in order to disintegrate the coarser particles of the nitropyrimidine. In about 30 minutes the nitropyrimidine had completely dissolved and the reduction was complete. During the reduction we did not detect the presence of ammonia, but after the reduction was finished it was noticeable, indicating a partial decomposition of the diamino derivative. In order to avoid decomposition we quickly filtered from aluminium hydroxide, when we obtained a clear, straw-colored solution. This gradually assumed a dark color when exposed to the air. In order to isolate the pyrimidine base, the solution was concentrated to a small volume by slow evaporation, under diminished pressure. The temperature was kept below 50° and a slow stream of dry hydrogen was passed continually through the capillary tube to avoid oxidation. Considerable amorphous material deposited. After concentrating to about 10 cc., the dark colored solution was filtered and allowed to stand in an ice chest, for 2 days. We obtained a deposit of amorphous substance associated with clusters of radiating prisms. The prisms were carefully removed and washed with cold water. They decomposed when heated above 230° and contained water of crystallization. For analysis they were dried in the atmosphere.

The water of crystallization was determined by heating at 120° – 130° , for 1 hour.

0.1124 gram substance lost 0.0163 gram H_2O .

	Calculated for $C_4H_6ON_4 \cdot H_2O$.	Found.
N	12.50	14.50

A determination of nitrogen in the anhydrous material gave the following result (Kjeldahl).

	Calculated for $C_4H_6ON_4$.	Found.
N	44.44	44.00

This base was, apparently, quite stable after drying in the air, but when dissolved in water it slowly decomposed with separation of amorphous material. It behaved in every respect like an orthodiamine. An aqueous solution of the base gave the following characteristic reactions: Potassiobismuth iodide

gave an insoluble, red precipitate; platinum and gold chlorides were reduced to metallic platinum and gold; Fehling's solution was reduced at once, and a silver mirror was formed when a solution of the base was added to an ammoniacal solution of silver nitrate.

An aqueous solution of the base gave an alkaline reaction when tested with turmeric and litmus. The base gave no difficultly soluble salts with nitric, hydrochloric and sulphuric acids. It was precipitated by phosphotungstic acid.

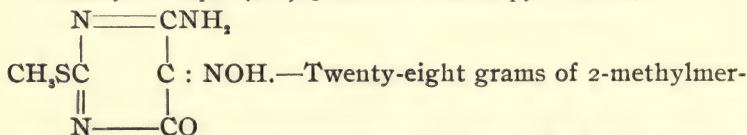
The Picrate of 2-Oxy-5,6-diaminopyrimidine.—This salt deposited from hot water in balls of microscopic prisms. The crystalline form resembled very much that of uracil. It had no definite melting point, but began to turn brown at about 170° , slowly decomposed on further heating, and did not effervesce at 300° . Analysis (Kjeldahl):

N	Calculated for $C_4H_6ON_4 \cdot C_6H_3O_7N_3$.	Found.	
		I.	II.
	27.60	27.67	27.50

The Mercuric Chloride Salt.—This was obtained when mercuric chloride was added to a solution of the base. Analysis (Kjeldahl):

N	Calculated for $C_4H_6ON_4 \cdot HgCl_2$.	Found.
	14.1	13.89

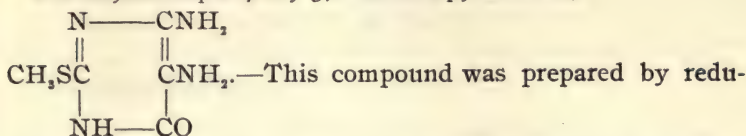
2-Methylmercapto-4-oxy-5-nitroso-6-aminopyrimidine,



capto-4-oxy-6-aminopyrimidine¹ and 7.2 grams of sodium hydroxide were dissolved in 450 cc. of water. To this solution was added a concentrated solution of 14 grams of sodium nitrite and then, slowly, 24 grams of glacial acetic acid. The mixture was allowed to stand for 2 hours, when the nitroso derivative deposited as a yellow, crystalline precipitate. After thoroughly washing with cold water, alcohol and ether the crude material was used for the following preparation:

¹ Johnson and Johns: *Loc. cit.*

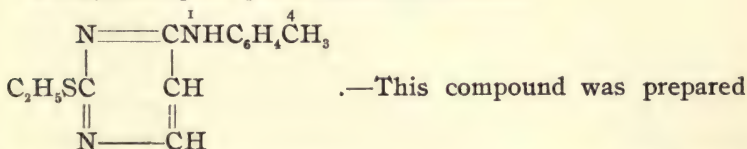
2-Methylmercapto-4-oxy-5,6-diaminopyrimidine,



cing the above nitroso derivative with ammonium sulphide. The base deposited from water in needle-like prisms that melted at $215^\circ\text{--}216^\circ$, with effervescence. It was very soluble in alcohol. It was unstable and gradually assumed a red color when exposed to the air. Analysis (Kjeldahl) :

	Calculated for $\text{C}_5\text{H}_8\text{ON}_4\text{S}$.	Found.
N	32.55	32.15

2-Ethylmercapto-6-paratoluidinopyrimidine,

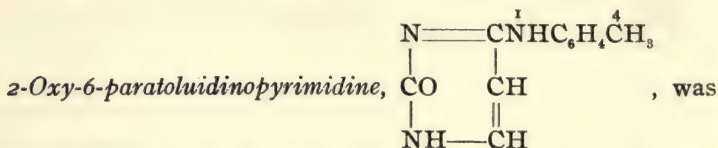


by dissolving 2-ethylmercapto-6-chlorpyrimidine and paratoluidine in dry benzene, in the proper proportions, and warming the solution for several hours on the steam-bath. The excess of benzene was then evaporated on the steam-bath and the pyrimidine purified in the form of its hydrochloride. This deposited from dilute hydrochloric acid in needles that decomposed at $198^\circ\text{--}207^\circ$, with effervescence. The salt was soluble in hot alcohol and deposited, on cooling, in needles. Analysis (Kjeldahl) :

	Calculated for $\text{C}_{13}\text{H}_{16}\text{N}_6\text{S.HCl}$.	Found.
N	14.92	14.87

The free base was obtained when the hydrochloride was treated with aqueous ammonia. It separated as a pasty mass, which finally solidified. It deposited from petroleum ether in prismatic crystals that melted, at 104° , to a clear oil. They were extremely soluble in alcohol and benzene. Analysis (Kjeldahl) :

	Calculated for $C_{13}H_{16}N_3S$.	Found.
N	17.14	16.93



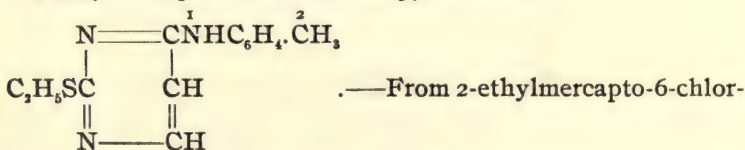
obtained in the form of its hydrochloride by boiling 2-ethylmercapto-6-paratoluidinopyrimidine with concentrated hydrochloric acid until ethylmercaptan ceased to be evolved. It deposited from alcohol in microscopic prisms that decomposed between 180° – 190° , with effervescence. It was soluble in hot water. Analysis (Kjeldahl) :

	Calculated for $C_{11}H_{11}ON_3.HCl$.	Found.
N	17.68	17.81

When an aqueous solution of this hydrochloric acid salt was treated with ammonia the free base separated as a crystalline precipitate. It was insoluble in hot water and the ordinary organic solvents, but was purified for analysis by prolonged extraction with hot water. It decomposed slowly when heated above 280° and then melted, to a dark colored oil, at 288° – 289° , with violent effervescence. Analysis (Kjeldahl) :

	Calculated for $C_{11}H_{11}ON_3$.	Found.
N	20.89	20.71

2-Ethylmercapto-6-orthotoluidinopyrimidine,

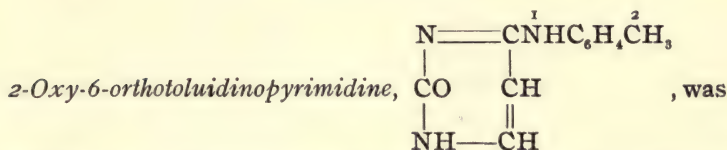


pyrimidine and orthotoluidine. Its hydrochloride deposited from dilute hydrochloric acid in granular crystals that melted at 230° – 232° , with effervescence. Analysis (Kjeldahl) :

	Calculated for $C_{13}H_{16}N_3S.HCl$.	Found.
N	14.92	14.63

When an aqueous solution of the hydrochloride was treated with ammonia the base separated as an oil which solidified on standing. It deposited from alcohol in prisms that melted, at 87°, to a clear oil. Analysis (Kjeldahl) :

	Calculated for $C_{13}H_{15}N_3S$.	Found.
N	17.14	17.04



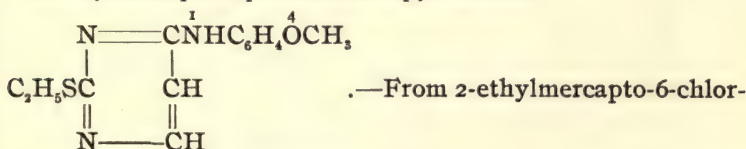
prepared by boiling 2-ethylmercapto-6-orthotoluidinopyrimidine with hydrochloric acid. The hydrochloride was very soluble in water but insoluble in benzene and acetone. It was purified for analysis by crystallizing from 95 per cent alcohol. It deposited in lenticular shaped crystals that decomposed at 227°-231°, with effervescence. Analysis (Kjeldahl) :

	Calculated for $C_{11}H_{11}ON_3.HCl$.	Found.
N	17.68	17.35

The pyrimidine base was insoluble in cold water. It deposited from hot water in radiating prisms that decomposed at 262°. Analysis (Kjeldahl) :

	Calculated for $C_{11}H_{11}ON_3$.	Found.
N	20.89	21.05

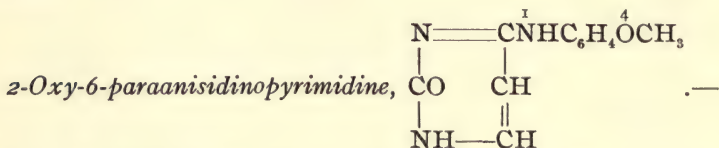
2-Ethylmercapto-6-paraanisidinopyrimidine,



pyrimidine and paraanisidine. The hydrochloride of this base deposited from hot water in needles that melted at 200°-201°, with effervescence, to an oil. Analysis (Kjeldahl) :

	Calculated for $C_{13}H_{15}ON_3S.HCl$.	Found.
N	14.11	14.11

When the salt was treated with ammonia the base was obtained as an oil, that did not solidify after standing for several weeks.



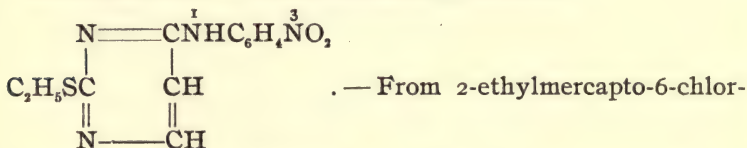
The hydrochloride deposited from water in small, radiating needles. It was purified for analysis by recrystallizing from alcohol that was acidified with hydrochloric acid. It decomposed between 145° and 165° , with effervescence. Analysis (Kjeldahl):

	Calculated for $\text{C}_{11}\text{H}_{11}\text{O}_2\text{N}_3\cdot\text{HCl}$.	I.	Found.	II.
N	16.56	16.72		16.65

The free base was difficultly soluble in all ordinary media and showed no crystalline form. It was purified for analysis by drying at 110° , for 2 hours. It melted at 262° . Analysis (Kjeldahl):

	Calculated for $\text{C}_{11}\text{H}_{11}\text{O}_2\text{N}_3$.	I.	Found.	II.
N	19.35	19.68		19.53

2-Ethylmercapto-6-metanitroanilinopyrimidine,



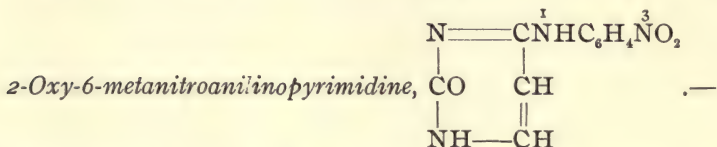
pyrimidine and metanitroaniline. In this experiment we observed that the free base could be more easily purified than its hydrochloric acid salt. It was insoluble in water and soluble in alcohol. It melted at 175° . Analysis (Kjeldahl):

	Calculated for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_4\text{S}$.	I.	Found.	II.
N	20.29	20.6		20.13

The hydrochloride was prepared by dissolving the base in dilute hydrochloric acid. It deposited in needles that decom-

posed at 140°–155°, with effervescence. Analysis (Kjeldahl):

N	Calculated for $C_{12}H_{12}O_2N_4S \cdot HCl$.	Found.	
	17.92	I. 17.5	II. 17.67



This compound could not be obtained in the usual manner by boiling the above 2-ethylmercapto-6-metanitroanilinopyrimidine with hydrochloric acid. The mercaptopyrimidine was recovered unaltered after boiling with concentrated hydrochloric acid for 15 hours. In order to remove the mercapto radical it was necessary to boil with hydrobromic acid. The hydrobromide was purified by crystallization from 95 per cent alcohol. It decomposed between 160° and 180°, with effervescence. When the salt was treated with alcoholic ammonia the pyrimidine base separated in needle-like prisms. They decomposed when heated above 275°. Analysis (Kjeldahl):

N	Calculated for $C_{10}H_8O_2N_4$.	Found.
	24.14	24.35

NEW HAVEN, CONN.,
June 1, 1906.

III. RESEARCHES ON PYRIMIDINS: 5-ETHYLCYTOSIN.

(Eighteenth Paper.)

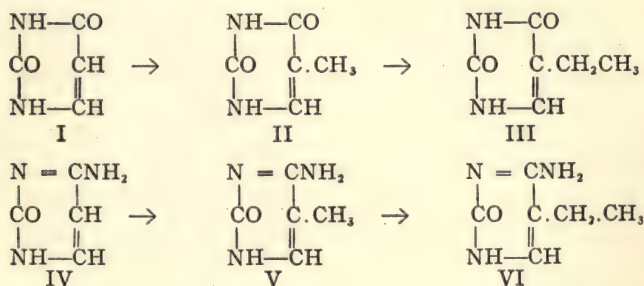
BY TREAT B. JOHNSON AND GEORGE A. MENGE.

(From the Sheffield Laboratory of Yale University.)

(Received for publication, May 13, 1906.)

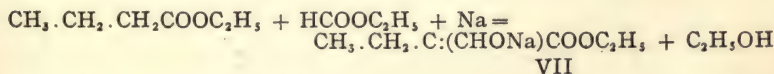
Methods of synthesizing uracil, I, thymin, II, cytosin, IV, and 5-methylcytosin, V, have been described in previous papers from this laboratory.¹

Thymin, II, and 5-methylcytosin, V, are the simplest mono-5-alkyl derivatives of uracil, I, and cytosin, IV, respectively. They may be considered as the second members of two homologous series of which uracil, I, and cytosin, IV, are the primary substances.



The work described in this paper was undertaken with the object of preparing 5-ethyluracil, III, and 5-ethylcytosin, VI, the third homologues of these two series.

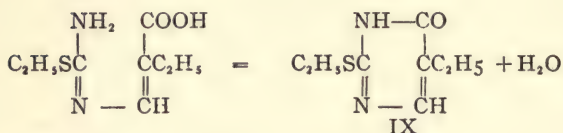
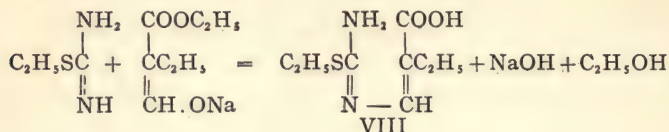
We find that ethylformate condenses with normal ethylbutyrate in the presence of sodium ethylate, or metallic sodium, to form the sodium salt of ethyl formylbutyrate, VII:



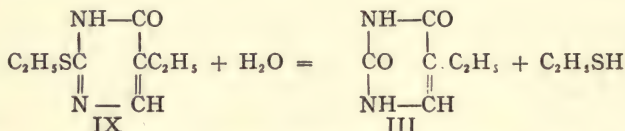
When this sodium salt, VII, was dissolved in water with the

¹ Wheeler and Merriam, *Amer. Chem. Jour.*, xxix, p. 478, 1903; Wheeler and Johnson, *ibid.*, xxix, p. 492, 1903; *ibid.*, xxxi, p. 591, 1904.

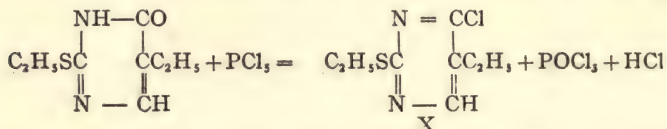
calculated quantity of pseudoethylthiourea they condensed to form 2-ethylmercapto-5-ethyl-6-oxypyrimidin, IX. This condensation involves the intermediate formation of α -ethyl- β -pseudoethylthioureaacrylic acid, VIII. We have succeeded in isolating this compound.



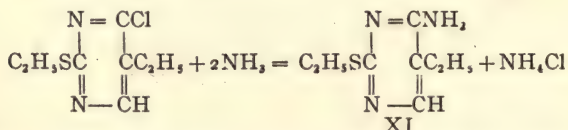
Practically a quantitative yield of 5-ethyluracil, III, was obtained when this mercaptopyrimidin, IX, was boiled with hydrobromic acid:



When 2-ethylmercapto-5-ethyl-6-oxypyrimidin, IX, was heated on the steam-bath with phosphorus pentachloride it was converted into 2-ethylmercapto-5-ethyl-6-chlorpyrimidin, X:

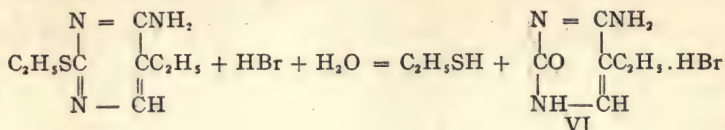


This mercaptochlorpyrimidin, X, then gave a quantitative yield of 2-ethylmercapto-5-ethyl-6-aminopyrimidin, XI, when heated with alcoholic ammonia:

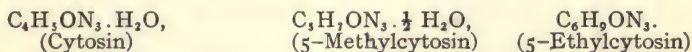


Finally this 2-ethylmercapto-5-ethyl-6-aminopyrimidin, XI

was converted into the hydrobromide of 5-ethylcytosin, VI, by boiling with hydrobromic acid.



5-Ethylcytosin, VI, separates from water without water of crystallization. This property is of especial interest. Cytosin, IV, and 5-methylcytosin, V, the preceding members of the same series, crystallize with one molecule and a half molecule of water of crystallization respectively.



5-Ethylcytosin is more soluble in water than cytosin, and less soluble than 5-methylcytosin. It forms normal salts (1:1) with hydrochloric, hydrobromic, and nitric acids.

One of the most characteristic properties of 5-methylcytosin was its tendency to form basic salts¹ with hydrobromic and hydrochloric acids. We now find that 5-ethylcytosin likewise possesses this interesting property. When ammonia was added to an aqueous solution of the hydrobromide we obtained a mixture of two hydraous, basic salts. Our analytical determinations indicated that we were dealing with a 2:1, XII, and a 3:1 hydrobromide, XIII. On account of the small amount of 5-ethylcytosin at our disposal we were unable to make as thorough a study of these basic salts as we desired.



5-Ethylcytosin is precipitated by phosphotungstic acid. The amino radical is more firmly linked in this base than in cytosin and 5-methylcytosin. While the latter two bases are converted into uracil and thymine when heated with 20 per cent. sulphuric acid, 5-ethylcytosin was recovered unaltered when treated under the same conditions.

¹ Wheeler and Johnson, *loc. cit.*

TABLE OF THE SALTS OF CYTOSIN, 5-METHYLCYTOSIN AND 5-ETHYLCYTOSIN WITH THE COMMON INORGANIC ACIDS: ALSO SOLUBILITY OF THESE BASES IN WATER AT 25° C. AND WATER OF CRYSTALLIZATION.

Base	HCl Salts	HBr Salts	HNO ₃ Salts	H ₂ SO ₄ Salts	Water of Crystallization	Solubility in Water at 25° C
$\begin{array}{c} \text{N} = \text{C} \cdot \text{NH}_2 \\ \\ \text{CO} \quad \text{CH} \\ \\ \text{NH} - \text{CH} \\ \\ \text{(Cytosin)} \end{array}$	$(\text{C}_4\text{H}_5\text{ON}_3)_2 \cdot 2\text{HCl}^*$		$(\text{C}_4\text{H}_5\text{ON}_3) \cdot \text{HNO}_3^\dagger$	$\begin{array}{l} (\text{C}_4\text{H}_5\text{ON}_3) \cdot \text{H}_2\text{SO}_4^\dagger \\ (\text{C}_4\text{H}_5\text{ON}_3)_2 \cdot \text{H}_2\text{SO}_4^{**} \\ (\text{C}_4\text{H}_5\text{ON}_3)_4 \cdot \text{H}_2\text{SO}_4^\dagger \\ (\text{C}_4\text{H}_5\text{ON}_3)_4 \cdot \text{H}_2\text{SO}_4 \cdot 2\text{H}_2\text{O}^{\dagger\dagger} \end{array}$	H_2O	100 parts of water dissolve 0.8 parts of base.
$\begin{array}{c} \text{N} = \text{C} \cdot \text{NH}_2 \\ \\ \text{CO} \quad \text{C} \cdot \text{CH}_3 \\ \\ \text{NH} - \text{CH} \\ \\ \text{(5-Methylcytosin)} \end{array}$	$\begin{array}{l} (\text{C}_5\text{H}_7\text{ON}_3) \cdot \text{HCl}^* \\ (\text{C}_5\text{H}_7\text{ON}_3) \cdot \text{HCl} \cdot 2\text{H}_2\text{O}^* \\ (\text{C}_5\text{H}_7\text{ON}_3)_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}^* \\ (\text{C}_5\text{H}_7\text{ON}_3)_5 \cdot 2\text{HCl} \cdot 3\text{H}_2\text{O}^* \end{array}$	$(\text{C}_5\text{H}_7\text{ON}_3)_2 \cdot \text{HBr} \cdot \text{H}_2\text{O}^*$			$\frac{1}{3}\text{H}_2\text{O}$	100 parts of water dissolve 4.5 parts of base.
$\begin{array}{c} \text{N} = \text{C} \cdot \text{NH}_2 \\ \\ \text{CO} \quad \text{C} \cdot \text{C}_2\text{H}_5 \\ \\ \text{NH} - \text{CH} \\ \\ \text{(5-Ethylcytosin)} \end{array}$	$(\text{C}_6\text{H}_9\text{ON}_3) \cdot \text{HCl}^\dagger$	$\begin{array}{l} (\text{C}_6\text{H}_9\text{ON}_3) \cdot \text{HBr}^\dagger \\ (\text{C}_6\text{H}_9\text{ON}_3)_2 \cdot \text{HBr} \cdot \text{H}_2\text{O}^\dagger \\ (\text{C}_6\text{H}_9\text{ON}_3)_3 \cdot \text{HBr} \cdot \text{H}_2\text{O}^\dagger \end{array}$	$(\text{C}_6\text{H}_9\text{ON}_3) \cdot \text{HNO}_3^\dagger$		No water	100 parts of water dissolve 1.33 parts of base.

*Wheeler and Johnson, *Amer. Chem. Jour.*, xxxi, p. 598.

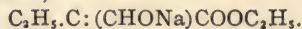
†Johnson and Menge, this paper.

‡Kossel and Steudel, *Zeitschr. f. physiol. Chem.*, xxxviii, p. 52.

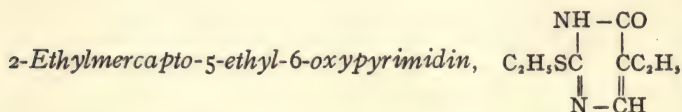
**Levene, *ibid.*, xxxvii, p. 405.

††Levene, *ibid.*, xxxix, pp. 7, 135, 481.

EXPERIMENTAL PART.

Sodium Salt of Ethyl Formylbutyrate,

This salt can be prepared very easily by proceeding in the following manner: A known weight of alcohol-free sodium ethylate was suspended in dry ether. A mixture of the calculated quantities of ethylformate and ethylbutyrate was then added to the ether and the condensation allowed to proceed at ordinary temperature. Sufficient heat was evolved to cause the ether to boil. The mixture was allowed to stand for four days when the excess of ether was removed by sucking a current of dry air through the solution. We obtained a thick oil which immediately solidified to a solid cake when treated with a little water. No further purification was attempted. This salt was dissolved in cold water and the solution washed with ether to remove any unaltered esters. This solution was then used for the condensations described in this paper. In our calculations we have assumed that the sodium salt is formed in practically theoretical amount.



One hundred and fifty grams of normal ethylbutyrate were condensed with ethylformate in presence of sodium ethylate as described in the preceding experiment. The resulting sodium salt of ethyl formylbutyrate was then dissolved in water, and treated with an aqueous solution of 0.5 molecular proportion of pseudoethylthiourea. This was prepared by dissolving 119 grams of the hydrobromide in ice water and neutralizing the hydrobromic acid with 36 grams of potassium hydroxide. The alkaline solution was allowed to stand over night at ordinary temperature and then heated on the steam-bath for about two hours. The solution was then filtered and acidified with acetic acid. The mercaptopyrimidin separated at once as a flocculent precipitate. After drying over sulphuric acid the crude material weighed 40 grams, corresponding to 38 per cent. of the theoretical.

calculating from the weight of pseudourea used. It was extremely soluble in alcohol and benzene, and moderately soluble in ether. It was difficultly soluble in water. It deposited from hot water or dilute alcohol in well developed prisms that melted at $119-120^{\circ}\text{C.}$ to a clear oil. Analysis (Kjeldahl):

Calculated for $\text{C}_8\text{H}_{12}\text{ON}_2\text{S}$:
N = 15.17 per cent.

Found:
15.12 per cent.

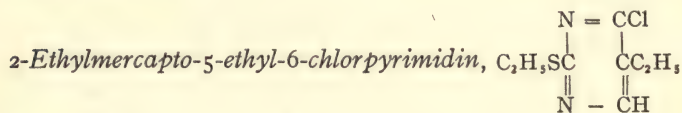
α -Ethyl- β -pseudoethylthioureaacrylic acid,



This was obtained as an intermediate product in the preceding condensation. After filtering from the 2-ethylmercapto-5-ethyl-6-oxypyrimidin the acetic acid filtrate was concentrated on the steam-bath and then allowed to stand at ordinary temperature for several hours. A heavy, flocculent precipitate separated on cooling. The substance was very soluble in alcohol. When heated above its decomposition point it was converted into the mercaptopyrimidin above. It deposited from hot alcohol in plates that melted at $148^{\circ}-149^{\circ}\text{C.}$, with effervescence, to a clear oil. When this oil was allowed to cool below 100°C. it solidified. Upon heating again in the capillary tube it melted at $117^{\circ}-118^{\circ}\text{C.}$ to a clear oil. Analysis (Kjeldahl):

Calculated for $\text{C}_8\text{H}_{14}\text{O}_2\text{N}_2\text{S}$:
N = 13.86 per cent.

Found:
13.70 per cent.

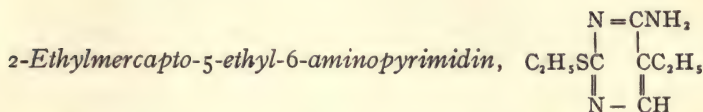


Twenty-five grams of 2-ethylmercapto-5-ethyl-6-oxypyrimidin and a slight excess over one molecular proportion of phosphorus pentachloride were mixed in a flask and gently heated on the steam-bath. A violent reaction took place with evolution of hydrochloric acid gas. We obtained a dark colored liquid that was heated for several minutes at 100°C. to complete the reaction. The liquid was then poured upon crushed ice to decompose the phosphorus halides. The chlorpyrimidin was extracted with ether, dried over calcium chloride, and purified by distillation under diminished pressure. It boiled at $160^{\circ}-163^{\circ}\text{C.}$

under 24 mm. pressure. It would not solidify in a freezing mixture. The yield of pure distilled material was 14 grams, or about 54 per cent. of the theoretical. When boiled with water it was converted into the original 2-ethylmercapto-5-ethyl-6-oxy-pyrimidin. Analysis (Kjeldahl):

Calculated for $C_8H_{11}N_2SCl$:
N = 13.8 per cent.

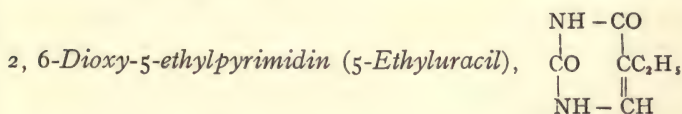
Found:
13.43 per cent.



This aminopyrimidin was obtained when the chlorpyrimidin above was heated in a sealed tube with alcoholic ammonia at 130°–140° C. for two hours. The excess of ammonia and alcohol was then removed by evaporation on the steam-bath. The residue was then treated with water to remove ammonium chloride. We obtained an oil that was very soluble in ether. When the ether solution was allowed to evaporate spontaneously the aminopyrimidin deposited in prismatic crystals. It was insoluble in ligroin but extremely soluble in benzene. It deposited from a mixture of these two solvents in stout prisms that melted at 74°–76° C. to an oil. Analysis (Kjeldahl):

Calculated for $C_8H_{13}N_3S$:
N = 22.95 per cent.

Found:
22.88 per cent



This pyrimidin was prepared by boiling 2-ethylmercapto-5-ethyl-6-oxy-pyrimidin with hydrobromic acid. It was difficultly soluble in water. One part of the pyrimidin dissolved in about 625 parts of water at 25° C. It deposited from hot water in balls of microscopic prisms that melted at about 300° C. with decomposition. Analysis (Kjeldahl):

Calculated for $C_8H_9O_2N_2$:
N = 20.0 per cent.

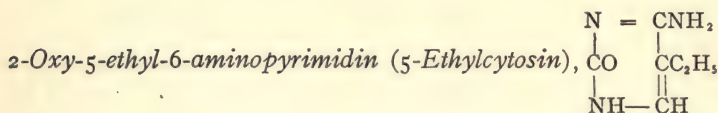
Found:
19.8 per cent.

5-Ethylcytosin Monohydrobromide (Anhydrous).

This salt was obtained when 2-ethylmercapto-5-ethyl-6-amino-pyrimidin was boiled with hydrobromic acid. When the acid solution was allowed to stand, the hydrobromide deposited in large prisms. They did not contain water of crystallization. When heated in a capillary tube the salt began to darken at about 265° and melted at 284°–286° C. with effervescence. Analysis (Kjeldahl):

Calculated for $C_8H_{10}ON_3 \cdot HBr$:
N = 19.13 per cent.

Found:
19.2 per cent.



In order to obtain this base, the monohydrobromide, described above, was dissolved in water; the bromide was removed by means of silver sulphate; the excess of silver was precipitated with hydrogen sulphide, the sulphuric acid by barium hydroxide, and then the excess of barium with carbon dioxide. The clear solution was then concentrated to a small volume, whereupon on cooling the base deposited in beautiful, slender prisms. They did not contain water of crystallization. One part of the base dissolved in about 75 parts of water at 25° C. When heated in a capillary tube it melted with effervescence at 282°–283° C. Analysis (Kjeldahl):

Calculated for $C_8H_{10}ON_3$:
N = 30.21 per cent.

Found:
30.03 per cent.

The base was precipitated from its aqueous solution by mercuric chloride and phosphotungstic acid. The phosphotungstate was soluble in boiling water and deposited again on cooling. When a solution of the pyrimidin base was treated with a solution of potassio-bismuth iodide a red precipitate was obtained. It was insoluble in hot water.

5-Ethylcytosin was heated with 20 per cent. sulphuric acid for six hours at 140°–150° C. When the pressure tube was examined there was no apparent decomposition. Upon concentrating on the steam-bath we did not obtain a deposit of 5-ethyluracil. The sulphuric acid was removed with barium hydroxide, and the

excess of alkali with carbon dioxide. When the neutral solution was concentrated to a small volume, the unaltered base deposited in characteristic, slender prisms that melted at 282° – 283° C. with effervescence. When mixed with the original base the melting-point was not lowered.

Platinum Chloride Double Salt.

This salt was extremely soluble in water. It deposited from hot water in radiating, transparent prisms. A nitrogen determination gave the following result:

Calculated for $(C_5H_9ON_3)_2 \cdot H_2PtCl_6 \cdot 2H_2O$:
N = 11.62 per cent.

Found:
11.56 per cent

The Picrate of 5-Ethylcytosin.

This salt was prepared by treating a solution of the base with picric acid. It was difficultly soluble in water. It deposited from hot water in yellow, opaque crystals. When heated in a capillary tube they decomposed at 277° – 278° C.

5-Ethylcytosin Monohydrochloride (Anhydrous).

This salt was prepared by dissolving 5-ethylcytosin in dilute hydrochloric acid and allowing the solution to slowly evaporate in a desiccator over sulphuric acid. It deposited in flat prisms. They were extremely soluble in cold water and melted at 238° – 240° C. with slight effervescence. Analysis (Kjeldahl):

Calculated for $C_5H_9ON_3 \cdot HCl$:
N = 23.93 per cent.

Found:
23.90 per cent.

Nitrate of 5-Ethylcytosin.

Obtained by allowing a nitric acid solution of the base to slowly evaporate in a desiccator over sulphuric acid. It deposited in stout prisms. They decomposed at about 170° – 172° C. The salt was very soluble in cold water. Analysis (Kjeldahl):

Calculated for $C_5H_9ON_3 \cdot HNO_3$:
N = 27.72 per cent.

Found:
27.39 per cent.

Basic Hydrobromides of 5-Ethylcytosin.

Some of the 2-ethylmercapto-5-ethyl-6-aminopyrimidin was boiled with hydrobromic acid until ethyl mercaptan ceased to be evolved. The solution was then evaporated to dryness to remove the excess of acid. Upon adding ammonia to an aqueous solution

of the hydrobromide we obtained an immediate precipitate in the form of well developed prisms. This precipitate was difficultly soluble in water. It deposited from hot water in clusters of radiating prisms associated with diamond-shaped crystals. They decomposed at 258° – 260° C. with violent effervescence. We were unable to raise this decomposition point by repeated recrystallizations from hot water. The material gave a strong test for bromine. The analytical determinations indicated that we were not dealing with a homogeneous salt, but a mixture of two hydrous, basic salts. Our determinations agreed with the calculated values for a mixture of about equal proportions of a 2:1 and a 3:1 hydrobromide.

0.3358 gram of substance lost 0.0127 gram on heating to constant weight at 100° – 110° C.

For $(C_6H_9ON_3)_2 \cdot HBr \cdot H_2O$ —

Calculated: H_2O = 4.8 per cent.

For $(C_6H_9ON_3)_3 HBr \cdot H_2O$ —

Calculated: H_2O = 3.4 per cent.

Average: H_2O = 4.1 per cent.

Found: H_2O = 3.78 per cent.

Nitrogen determinations in the hydrous material (Kjeldahl):

For $(C_6H_9ON_3)_2 \cdot HBr \cdot H_2O$ —

Calculated : N = 22.31 per cent.

For $(C_6H_9ON_3)_3 \cdot HBr \cdot H_2O$ —

Calculated: N = 24.41 per cent.

Average : N = 23.36 per cent.

Found : N = (1) 23.29; (2) 23.31 per cent.

Nitrogen determinations in the anhydrous material (Kjeldahl):

For $(C_6H_9ON_3)_2 \cdot HBr$ —

Calculated : N = 23.39 per cent.

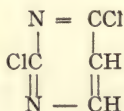
For $(C_6H_9ON_3)_3 \cdot HBr$ —

Calculated : N = 25.30 per cent.

Average : N = 24.34 per cent.

Found : N = (1) 24.48; (2) 24.07 per cent.

2, 6-Dichlorpyrimidin,



This compound has been described by Gabriel.¹ He prepared

¹*Ber. d. deutsch. chem. Gesellsch.*, xxxviii, p. 1690, 1905.

it by heating uracil with phosphorus oxychloride at 140°C . He states that it melted at 61°C . and boiled at $208.5^{\circ}\text{--}209.5^{\circ}\text{C}$. at 773 mm. We had prepared the same chloride, previous to this publication, by warming 2-thiouracil¹ on the steam-bath with phosphorus pentachloride. From 35 grams of 2-thiouracil we obtained 19.2 grams of the dichlorpyrimidin boiling at 101°C . at 23 mm. In another experiment we obtained 13 grams from 20 grams of 2-thiouracil. It boiled at 198°C . at 760 mm. Our compound melted at 63°C . to a clear oil. It was soluble in alcohol, benzene, and ether. Its vapors attacked the eyes. Analysis (Kjeldahl):

Calculated for $\text{C}_4\text{H}_2\text{N}_2\text{Cl}_2$:

N = 18.79 per cent.

Found:

18.78 per cent.

¹Wheeler and Bristol, *Amer. Chem. Jour.* xxxiii, p. 458, 1905.

[Reprinted from the American Chemical Journal, Vol. XXXVII. No. 4.
April, 1907.]

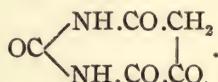
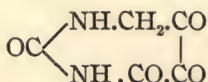
Contributions from the Sheffield Laboratory of Yale University.

CXLII.—RESEARCHES ON PYRIMIDINES: SYNTHESIS OF URACIL-5-CARBOXYLIC ACID.

[NINETEENTH PAPER.]

BY HENRY L. WHEELER, TREAT B. JOHNSON, AND CARL O. JOHNS.

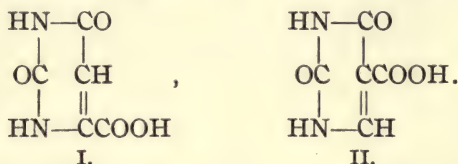
A new substance, having acid properties, called orotic acid (*Acido orotico*) has been isolated by Biscaro and Belloni¹ from milk. They assign to this compound the empirical formula, $C_5H_4O_4N_2.H_2O$, and believe that its structure is to be represented by one of the following formulas:



¹ *Annuario della Soc. Chimica di Milano*, XI, fasc. I (1905); *Ibid.*, XI, fasc. II (1905)
Vide also Centrabl., 1905, I, 63, 64. We take this occasion to thank the above authors for sending us reprints of these two articles.

It seemed to us that instead of a ring with 7 members, one with 5 or 6 would most probably prove to be correct. The properties of the substance and the fact that it gives urea on oxidation, suggested that it might be a pyrimidine.

The above empirical formula is that of a uracil carboxylic acid having a molecule of water of crystallization. There are 2 uracil carboxylic acids which have the acid group attached to carbon, namely, the 4- (I.) and 5- (II.) derivatives,



As neither of these acids have hitherto been prepared, a description is now given of the preparation and properties of the latter acid, while an account of uracil-4-carboxylic acid will appear in a later article. The study of these acids, and also the carboxyl derivatives of thymine and cytosine, is of interest on account of the possibility that in the nucleic acids uracil, thymine and cytosine may exist as carboxyl derivatives, being held together not alone by means of phosphorus atoms, as suggested by Bang¹ and Osborne and Harris,² but also by an acid amide or polypeptide grouping as in the case of the proteids. In such an event the means hitherto used to disrupt the nucleic acid molecule must also cause a loss of the carboxyl group from the pyrimidines. In this connection it is interesting to note that uracil-4-carboxylic acid can be heated with 20 per cent sulphuric acid, at 160°-170°, without alteration while, by such treatment, uracil-5-carboxylic acid is quantitatively converted into uracil. In fact, simply on prolonged boiling of this acid with hydrochloric acid it is converted into uracil. Uracil may, therefore, exist in the nucleic acids as a 5-carboxyl compound. We have shown that the pseudothiureas, H₂NC(SR) : NH, will react with aldehyde³

¹ Z. physiol. Chem., **31**, 425 (1900).

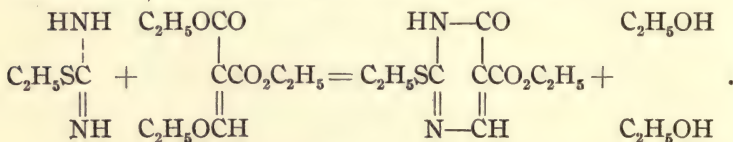
² Conn. Exper. Sta. Rep., 1901, p. 418.

³ THIS JOURNAL, **29**, 480 (1903).

and ketone esters to form pyrimidines in cases where urea refuses to act. According to Behrend the alkyl acetoacetic esters do not condense with urea.¹ We found that the methyl and ethyl derivatives give pyrimidines with the pseudothio-ureas. In that article we described 4,5-dimethyluracil as new, having missed the fact that Schlenker had obtained this substance by a different method.²

Another striking example of the difference between urea and a pseudothiurea was found when we tried the behavior of Claisen's ethoxymethylenemalonic ester³ toward these compounds. Urea showed no sign of reacting at 140° and a condensation was not effected on standing in alkaline solutions.

On the other hand, when ethoxymethylenemalonic ester was added to an alkaline, aqueous solution of ethylpseudothiurea hydrobromide,⁴ an immediate reaction took place and a salt of 2-ethylmercapto-5-carbethoxy-6-oxypyrimidine separated. This condensation can be represented as follows:



2-Ethylmercapto-5-carbethoxy-6-oxypyrimidine (I. see below) can be converted directly into uracil-5-carboxylic acid (IV.) by simply boiling with aqueous hydrochloric acid. When the mercapto ester (I.) is boiled, in alcoholic solution, with a small quantity of hydrochloric acid, uracil-5-ethylcarboxylate (II.) results. And this, on saponification, gives uracil-5-carboxylic acid. On the other hand, warm alkalis saponify the mercapto ester (I.) and give 2-ethylmercapto-5-carboxyl-6-oxypyrimidine (III.), which, with hot hydrochloric acid, gives uracil-5-carboxylic acid (IV.). When the acid (IV.) is melted it gives uracil (VI.).

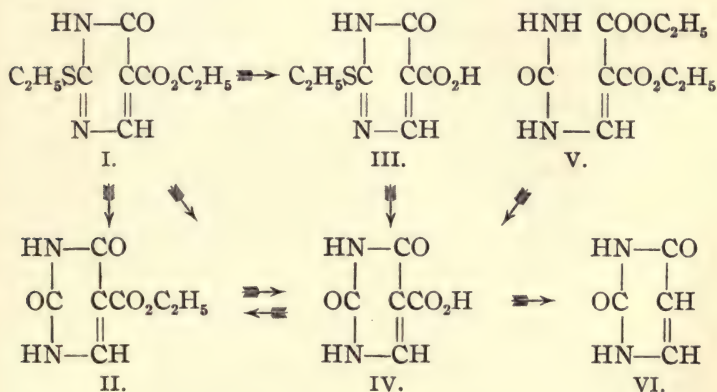
¹ Ann. Chem. (Liebig), **229**, 16 (1885).

² Ber. d. chem. Ges., **34**, 2812 (1901).

³ Ann. Chem. (Liebig), **297**, 75 (1897).

⁴ THIS JOURNAL, **29**, 483 (1903).

The formation of uracil, in this manner and also on heating with acids, shows that the condensation took place as represented in the above equation and that the product (I.) is not a barbituric acid derivative. In fact, we have not yet observed a satisfactory condensation of malonic ester, or any of its derivatives, with the pseudothiureas, to form barbituric acid derivatives. The substance represented by Formula V., uramidomethylenmalonic ester, was occasionally found as a by-product in the mother liquors of the condensation. On saponification it gave uracil-5-carboxylic acid. These compounds and their transformations can be represented as follows:



In some respects the properties of uracil-5-carboxylic acid agree closely with those of orotic acid. It is difficultly soluble in water, difficultly or insoluble in organic solvents and it crystallizes with the required 1 molecule of water of crystallization. Orotic acid is said to decompose at 260°. Our acid melts, with decomposition, at 278°. The potassium salt that crystallizes from solutions containing an excess of alkali is a monopotassium salt, $\text{C}_5\text{H}_3\text{O}_4\text{N}_2\text{K}$. Like orotic acid, our acid is dibasic and forms 2 series of salts. The potassium salt gives precipitates with barium chloride (crystalline), lead acetate and silver nitrate.

On the other hand, uracil-5-carboxylic acid differs from

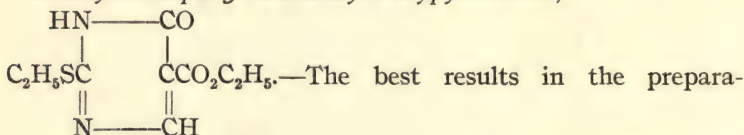
orotic acid as follows: It does not give a monosilver salt having the composition $C_5H_3O_4N_2Ag.H_2O$, which Biscaro and Belloni state is formed when silver nitrate is added to a solution of the monopotassium salt. In our case, when the monopotassium salt or alkali, acid and silver nitrate, in the proportion 1:1:1 were used, the silver salt formed was a disilver salt, a corresponding amount of acid remaining in the filtrate.

When methyl iodide was allowed to react, under pressure, on either mono or disilver orotate, Biscaro and Belloni obtained a monomethyl derivative melting at 248° – 250° . When we heated our silver salt with methyl iodide, in a closed tube at 100° , we obtained a mixture of substances from which a dimethyl derivative, melting about 254° – 256° , was isolated. Their monoethyl ester melted at 200° ; our product, obtained in like manner from the silver salt, melted at 162° – 163 , and the analysis showed that it was a diethyl derivative.

The free uracil-5-carboxylic acid does not give a precipitate with barium chloride, and we were unable to obtain a dichloride, which could be crystallized from boiling water without reverting to the acid, when the potassium salt was heated with phosphorus oxychloride.

EXPERIMENTAL PART.

2-Ethylmercapto-5-carbethoxy-6-oxyuracil,



tion of this substance were obtained as follows: Fifty-four grams of ethoxymethylenemalonate were added to a solution of 50 grams of ethylpseudothiourea hydrobromide in 50 cc. of water. To this mixture 30 grams of potassium hydroxide were slowly added and the solution was kept cold. The addition of alkali produced a yellow color and the solution became semisolid from the separation of a bulky, yellow precipitate. This impure potassium salt, when dry, weighed 58 grams, the yield being 87 per cent of the calculated, theory

requiring 66.5 grams. It crystallized from water in the form of colorless prisms and from alcohol in needles.

When a strong aqueous solution of the potassium salt was treated with dilute hydrochloric acid, avoiding an excess of acid, 2-ethylmercapto-5-carbethoxy-6-oxypyrimidine separated as a white, crystalline precipitate. This substance is readily soluble in hot alcohol and it separates in the form of long, slender, colorless prisms; from water it forms long, bulky, asbestos-like needles. It melts at 131° to a clear oil and it gave the following results on analysis (Kjeldahl):

	Calculated for $C_9H_{12}O_3N_2S$.	I.	Found.	II.
N	12.23	12.02		12.28

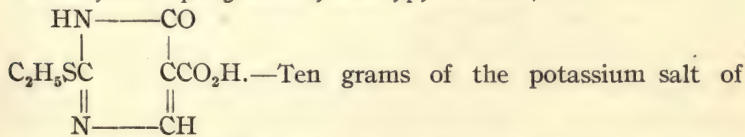
This ester dissolves in cold hydrochloric acid and is reprecipitated by ammonia. It has both acid and basic properties.

Uramidomethylenemalonic Ester, $H_2NCONHCH : C(CO_2C_2H_5)_2$.—This substance was obtained, in 2 experiments, by precipitating with hydrochloric acid, the filtrate from which the potassium salt of 2-ethylmercapto-5-carbethoxy-6-oxypyrimidine had separated. In the above case the amount obtained was 4.8 grams. It is very difficultly soluble in boiling water, readily soluble in hot alcohol; when crystallized from 50 per cent alcohol it forms bunches of colorless prisms melting at 206° , with effervescence. Nitrogen determinations gave (Kjeldahl):

	Calculated for $C_9H_{14}O_6N_2$.	I.	Found.	II.
N	12.17	12.22		12.06

This material has acid properties. When warmed with alkali, saponification takes place and hydrochloric acid then precipitates uracil-5-carboxylic acid.

2-Ethylmercapto-5-carboxyl-6-oxypyrimidine,



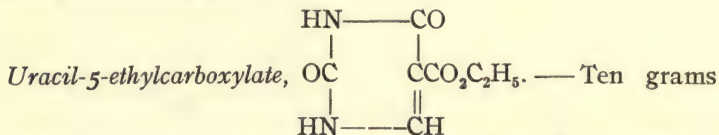
2-ethylmercapto-5-carbethoxy-6-oxypyrimidine were dissolved

in hot alcohol and a hot solution of 4.3 grams of potassium hydroxide, in a little water, were added. Saponification took place immediately and the solution became a thick jelly. The alcohol was then evaporated and the residue taken up in a little water. On adding an excess of hydrochloric acid a white precipitate of the mercapto acid separated. It weighed 7.1 grams, while the calculated is 7.5 grams, the yield being 94.6 per cent of theory.

This acid dissolves readily in hot alcohol, less readily in hot water, from which solvent it forms bunches of colorless, sharp-cornered plates. It melts to a clear oil at 167° and effervesces at a higher temperature. Nitrogen determination:

	Calculated for $C_7H_8O_5N_2S$.	Found.
N	14.00	13.72

This acid appears to be stronger than acetic acid, since it was not liberated from its potassium salt by means of an excess of acetic acid. It gives a bulky, white, gelatinous precipitate with alkali and silver nitrate. When warmed with hydrochloric acid, it readily evolves mercaptan and gives uracil-5-carboxylic acid.



of the potassium salt of 2-ethylmercapto-5-carbethoxy-6-oxypyrimidine were dissolved, or suspended, in about 75 cc. of strong alcohol, and about 5 cc. of concentrated hydrochloric acid were added. The whole was then boiled with a return condenser for several hours; the alcohol was evaporated and the residue was taken up in about 60 cc. of warm water. The hydrochloric acid was neutralized with ammonia and the solution was then filtered hot. On adding an excess of strong ammonia to the filtrate the ammonium salt of uracil-5-ethylcarboxylate separated as a sponge-like mass of long, slender, colorless needles. This was dissolved in about 50 cc. of water by warming and then a slight excess of acetic acid was added.

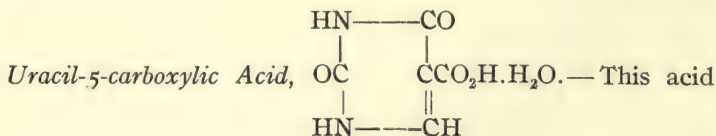
On cooling, a granular, crystalline precipitate of the free ester separated. This was found to be very soluble in hot water and moderately so in cold. It was difficultly soluble in alcohol. When crystallized from water it formed flat, sharp-pointed prisms, melting at 236° – 237° . Analysis:

	Calculated for $C_7H_8O_4N_2$.	I.	Found.
N	15.21	15.09	II. 15.21

The *ammonium salt* of uracil-5-ethylcarboxylate is characterized by some peculiar properties. When a not too dilute solution of the ester is treated with a little strong ammonia, long, slender needles of the ammonium salt form at once. The vapor from a rod dipped in ammonia and held above the surface of an aqueous solution of the ester will cause crystals to form. When a solution of the salt is boiled, ammonia escapes and, on cooling, nothing separates until more ammonia is added. If the solution is concentrated by heating, the free ester separates. The ammonium salt is insoluble, or difficultly soluble in alcohol. An aqueous solution of the ester was precipitated with ammonia and the precipitate was dried over calcium chloride. The needles thus obtained melted at about 220° to an oil that effervesced. Nitrogen determination (Kjeldahl):

	Calculated for $C_7H_8O_4N_2 \cdot NH_3 \cdot H_2O$.	Found.
N	19.13	19.33

When uracil-5-carboxylic ethyl ester is warmed with aqueous hydrochloric acid it is readily saponified and uracil-5-carboxylic acid is obtained.



can be prepared directly from the condensation product of ethoxymethylenemalonic ester and ethylpseudothiourea hydrobromide, or, in other words, from the potassium salt of 2-ethylmercapto-5-carbethoxy-6-oxypyrimidine, without the

isolation of the above intermediate products, by simply dissolving the salt in a moderate amount of strong hydrochloric acid and evaporating to dryness on the steam-bath. If the product contains sulphur, the operation is repeated. The residue is then crystallized from water as the acid is practically insoluble in alcohol. It is difficultly soluble in water and separates in the form of colorless, characteristic, minute pyramids with rough faces. Or small prisms form, the faces sometimes alternating with those of a pyramid. The crystals contain $1\text{H}_2\text{O}$, which is given off on heating above 100° . The acid melts partially, but quite sharply, at 278° , with energetic effervescence. The aqueous solution reddens litmus and it gives no immediate precipitate with lead or copper acetate, or barium chloride. Analysis:

I. 0.5002 gram substance, dried at about 50° , lost 0.0502 gram of water when heated for 1 hour at 122°

II. 0.5486 gram substance lost 0.0561 gram water when heated for 2 hours at 105° – 110° .

	Calculated for $\text{C}_6\text{H}_4\text{O}_4\text{N}_2 \cdot \text{H}_2\text{O}$.	I.	Found. II.	III.
H_2O	10.34	10.03	10.22	10.02
N	16.09	16.15	16.03	16.26

Nitrogen determination of the anhydrous acid:

	Calculated for $\text{C}_6\text{H}_4\text{O}_4\text{N}_2$.	I.	Found. II.	III.
N	17.94	17.88	17.99	17.91

Nitrogen was determined by Kjeldahl's method except in Analysis III. The acid used for Analysis III. (water) and Analysis VI. was obtained by the saponification of uramidomethylenemalonic ester. The other samples were obtained from the potassium salt described above.

Behavior on Heating.—About 0.5 gram of the acid was heated in a test tube, immersed in a sulphuric acid bath, at a temperature a little above its melting point until effervescence ceased. The dark-colored product was boiled with water and animal charcoal and the solution concentrated. On cooling, the characteristic crystals of uracil separated, melting or effervescing at 335° . Analysis (Kjeldahl):

	Calculated for $C_4H_4O_2N_2$.	Found.
N	25.00	24.89

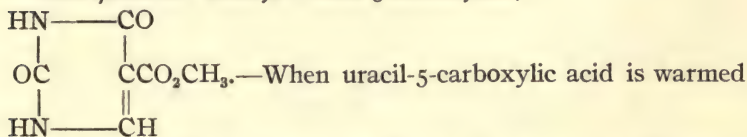
Action of Acids: Formation of Uracil.—The action of 20 per cent sulphuric acid was tried as follows: Fifty-five-hundredths gram of the acid potassium salt of uracil-5-carboxylic acid was sealed in a tube with 5 cc. of sulphuric acid, sp. gr. = 1.15, and heated at 160°–169° for 2 hours. On opening the tube, carbon dioxide escaped and the minute microscopic needles that had separated, after washing with water, were found to melt at 336° without further purification. A nitrogen determination agreed with the calculated for uracil:

	Calculated for $C_4H_4O_2N_2$.	Found.
N	25.00	24.97

The needles weighed 0.25 gram, which amount is 71 per cent of the calculated, or, allowing for solubility, it is practically a theoretical yield.

The Action of Concentrated Hydrochloric Acid.—One gram of uracil-5-carboxylic acid was boiled with about 50 cc. of concentrated hydrochloric acid, using a return condenser, for 18 hours. The acid was then evaporated and the residue was crystallized from water, whereupon over 0.3 gram of uracil separated.

Esterification: Methyl Uracil-5-carboxylate,



with acids in methyl or ethyl alcohol, it is smoothly esterified. One gram of the anhydrous acid was suspended in 75 cc. of methyl alcohol, to which 5 drops of concentrated sulphuric acid had been added. On boiling for 8 hours, all of the acid went into solution and on evaporation to a small volume a gelatinous mass was formed. This gave a white powder when stirred with cold water. The material thus obtained was readily soluble in hot water and on cooling, short, stout, color-

less prisms separated. These sintered at about 225° and decomposed at 233° . Nitrogen determination (Kjeldahl):

	Calculated for $C_6H_6O_4N_2$.	I.	Found.	II.
N	16.47	16.62		16.58

When uracil-5-carboxylic acid was warmed with ethyl alcohol and sulphuric acid, the ethyl ester described above was obtained. It was identified by the melting point 236° and by its behavior towards ammonia.

The Acid Potassium Salt, $C_5H_3O_4N_2K \cdot C_5H_4O_4N_2$.—When uracil-5-carboxylic acid and either sodium or potassium hydroxide were mixed, in molecular proportions, the hot aqueous solution, on cooling, deposited an acid salt. For example, 8 grams of the hydrous acid and 2.5 grams of potassium hydroxide were dissolved in about 500 cc. of boiling water. On cooling, 2 grams of slender, needle-like crystals separated. These effervesced at about 270° . Analysis:

	Calculated for $C_{10}H_7O_8N_4K$.	I.	Found.	II.	III.
N	16.00	15.89	15.98		
K	11.14				10.87

The Monopotassium Salt, $C_5H_3O_4N_2K$.—Three grams of uracil-5-carboxylic acid were dissolved in a solution of 2 grams of potassium hydroxide, 1.9 grams = 2 mols., in about 20 cc. of water; on concentrating on the steam-bath small needles separated. These were dried at about 55° . Nitrogen determinations (Kjeldahl):

	Calculated for $C_5H_3O_4N_2 \cdot K_2$.	Calculated for $C_5H_3O_4N_2K$.	I.	Found.	II.
N	12.06	14.43	14.72		14.71

The analyzed material showed no signs of melting at 295° . On dissolving the dried salt in water the solution was found to be neutral to litmus and turmeric. It gave a white, insoluble precipitate with lead acetate and the hot solution gave a crystalline precipitate with barium chloride.

The Barium Salt, $(C_5H_3O_4N_2)_2Ba$.—Barium chloride was added, in excess, to a hot, dilute, neutral solution of the above

potassium salt. Stout, microscopic prisms, pointed at both ends, crystallized out. These were almost insoluble in hot water. They were dried at 110°–120° but did not give off water.

	Calculated for $C_{10}H_6O_8N_4Ba$.	Found.
Ba	30.64	28.83

The Silver Salt.—Two grams of the monopotassium salt were dissolved in 100 cc. of water and 1.7 grams of silver nitrate in 50 cc. of water were slowly added, with stirring, in order to prevent a local excess of the nitrate. A white, bulky, gelatinous precipitate separated which did not alter or become granular on warming. The solution was diluted with 100 cc. of water and allowed to settle; the precipitate was washed by decantation and then filtered on cheese cloth. It was dried at 100° for analysis.

One molecular proportion more of silver nitrate was then added to the filtrate. This gave a slight precipitate. On adding 0.5 gram of potassium hydroxide, in a little water, a quantity of white salt was again precipitated, apparently equal in amount to that which was obtained at first. The analytical results did not agree with those calculated for a pure salt. They indicate that the precipitate was a mixture of a mono- and a disilver salt. A sample prepared by taking molecular proportions of acid, sodium hydroxide and silver nitrate gave no better results (Analyses III. and IV.).

	Calculated for $C_5H_3O_4N_2Ag$.	Calculated for $C_5H_2O_4N_2Ag_2$.	I.	Found. II.	III.	IV.
N	10.64	7.56	8.86	8.54		
Ag	41.64	58.37			49.0	51.5

The following shows that uracil-5-carboxylic acid gives a disilver salt: Eleven grams of the acid, dissolved in water and treated with 2 molecules of sodium hydroxide and 2 molecules of silver nitrate, gave a pure white precipitate which, when dry, weighed 21 grams. The calculated for a mono salt is 16 grams, that for a disilver salt is 23.4 grams.

Dimethyl Derivative.—Ten grams of the disilver salt were suspended in ether and 15 grams of methyl iodide were added.

The mixture was heated in a closed tube at 98° – 103° for 1.5 hours. The ether and excess of methyl iodide were evaporated and the residue extracted with alcohol. This gave a gummy extract which, when recrystallized from alcohol, yielded small prisms, melting at 254° – 256° , with slight effervescence. The substance dissolved with difficulty in hot alcohol and was moderately soluble in hot water. It had a very bitter taste. A nitrogen determination (Kjeldahl), made after drying at 110° – 120° , gave:

	Calculated for $C_7H_8O_4N_2$.	Found.
N	15.21	15.16

A *diethyl derivative* was prepared in a similar manner. It crystallized from alcohol, in which it is moderately soluble when cold, in the form of clusters of blunt prisms, melting at 162° – 163° . In both of these reactions of the silver salt the chief product isolated was the free, unaltered acid which was obtained by extracting the residue with water. A nitrogen determination (Kjeldahl), in the case of the material melting at 162° – 163° , showed that it was a diethyl derivative:

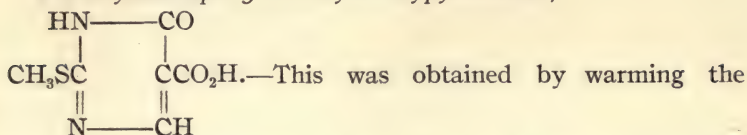
	Calculated for $C_9H_{12}O_4N_2$.	Found.
N	13.20	13.45

Ethoxymethylenemalonic ester and methyl pseudothio-urea hydriodide were condensed, using 1 molecular proportion of potassium hydroxide. Under these conditions the free 2-methylmercapto-5-carbethoxy-6-oxypyrimidine did not separate but, instead, a poor yield of a basic hydriodide of the ester was obtained. A nitrogen determination (Kjeldahl) agreed with the calculated for a 2:1 salt:

	Calculated for $(C_8H_{10}O_3N_2S)_2HI$.	Found.
N	10.0	10.1

This salt forms needles from alcohol; when boiled with water, mercaptan was given off. It had no definite melting point.

2-Methylmercapto-5-carboxyl-6-oxypyrimidine,



above salt with potassium hydroxide and then precipitating with hydrochloric acid. It crystallized from hot water in well developed, colorless prisms, melting, to a clear oil, at 235° . Nitrogen determination (Kjeldahl):

	Calculated for $\text{C}_6\text{H}_6\text{O}_3\text{N}_2\text{S}$.	Found.
N	15.05	14.71

Our chief experiments were performed with the ethylmercapto derivatives, since they are more insoluble than the methyl compounds.

NEW HAVEN, CONN.,
January, 1907.

[Reprinted from the American Chemical Journal, Vol. XXXVII, No. 6.
June, 1907.]

Contributions from the Sheffield Laboratory of Yale University.

CXLIV.—RESEARCHES ON PYRIMIDINES: SOME CONDENSATION PRODUCTS OF A SUBSTITUTED PSEUDOTHIOUREA: SYNTHESIS OF 1-METHYLURACIL.

BY TREAT B. JOHNSON AND F. W. HEYL.

(TWENTIETH PAPER.)

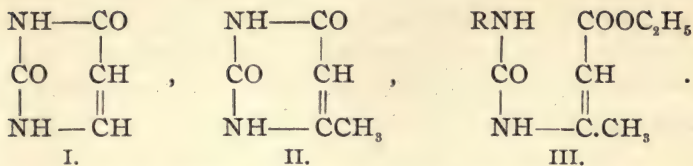
Substituted ureas apparently do not condense with β -ketone esters to form pyrimidines. While urea reacted with ethyl acetoacetate to form 4-methyluracil, II., Behrend¹ obtained no condensation products corresponding to methyluracil when phenylurea, diphenylurea and dimethylurea were treated with this ketone ester.

The alkyl derivatives of 4-methyluracil, II., in which the alkyl groups are linked to nitrogen, have all been prepared by heating this pyrimidine with alkyl halides² in presence of alkalis, or by condensing β -alkyluraminocrotonic esters, III., to pyrimidines, by treatment with alkali.³ The corresponding alkyl derivatives of uracil, I., have not been described.

¹ Ann. Chem. (Liebig), **229**, 15; **233**, 1.

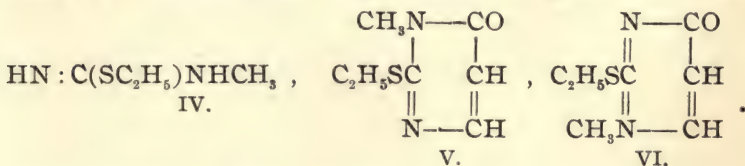
² Behrend: Ann. Chem. (Liebig), **229**, 23; **231**, 256; **253**, 67. Hagen: *Ibid.*, **244**, 2. Hoffman: *Ibid.*, **253**, 73. Behrend and Dietrich: *Ibid.*, **309**, 260. Behrend and Meyer: Ber. d. chem. Ges., **33**, 624.

³ Behrend and Meyer: Ber. d. chem. Ges., **33**, 621. Behrend and Buchholz: Ann. Chem. (Liebig), **314**, 209. Behrend and Thurm: *Ibid.*, **323**, 160. Behrend and Hesse: *Ibid.*, **329**, 341.

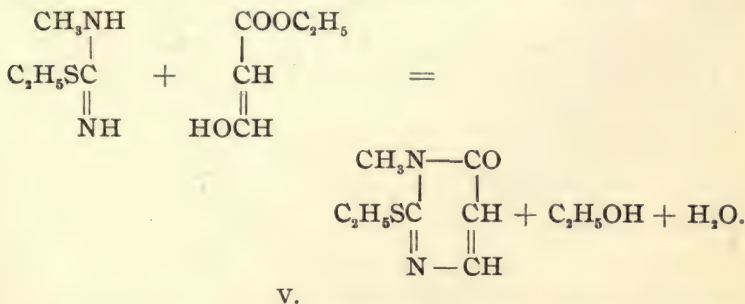


It has been shown in papers from this laboratory¹ that elementary pseudothioureas condense more readily with aldehyde and ketone esters than the normal oxygen ureas. In this paper we describe the behavior of an aliphatic, mono-substituted pseudothiourea towards some ketone esters. We find that they condense to give substituted mercaptopyrimidines, which are easily converted to uracil derivatives by digesting with hydrochloric acid.

Theoretically, 2 isomeric mercaptopyrimidines—1-methyl-2-ethylmercapto-6-oxypyrimidine, V., or 3-methyl-2-ethylmercapto-6-oxypyrimidine, VI., might be formed by condensing ethyl formylacetate with methyl pseudoethylthiourea, IV. We find that they condense to give 1-methyl-2-

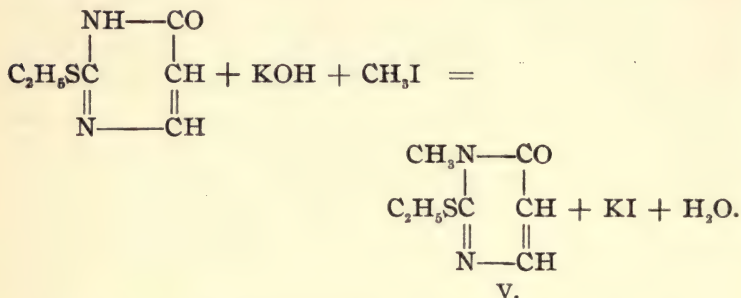


ethylmercapto-6-oxypyrimidine, V. We obtained no evidence of the formation of the isomeric derivative, VI.:

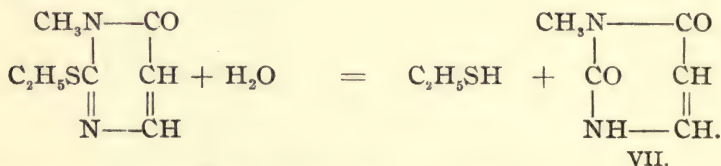


¹ Wheeler and Merriam: *THIS JOURNAL*, **29**, 478 (1903). Wheeler and Johnson: *Ibid.*, **31**, 591 (1904). Wheeler and Bristol: *Ibid.*, **33**, 437 (1905).

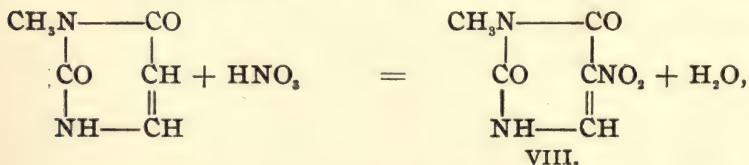
The same mercaptopyrimidine, V., was also obtained when 2-ethylmercapto-6-oxypyrimidine¹ was warmed in alcohol with molecular proportions of potassium hydroxide and methyl iodide.



When the mercaptopyrimidine, V., was digested with concentrated hydrochloric acid, it was converted quantitatively into 1-methyluracil, VII., with evolution of ethylmercaptan.



The structure of the methyluracil, VII., and the corresponding mercapto derivative, V., was shown in the following manner: It was converted smoothly into 1-methyl-2,6-dioxy-5-nitropyrimidine,² VIII., by treatment with fuming nitric and sulphuric acids. Our nitromethyluracil, VIII.,



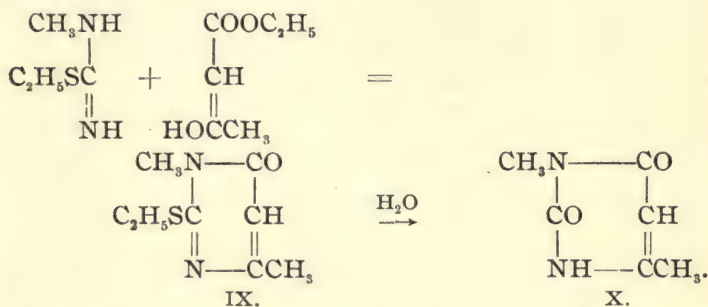
was anhydrous and melted at 264°–265°. The isomeric

¹ Wheeler and Merriam : *Loc. cit.*

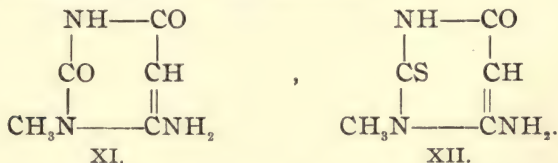
² Behrend and Thurm : *Loc. cit.*

3-methyl-2,6-dioxy-5-nitropyrimidine¹ contains 1 molecule of water of crystallization and melts at 255°–256°.

Methyl pseudoethylthiourea condensed with ethyl acetoacetate to give 1,4-dimethyl-2-ethylmercapto-6-oxypyrimidine, IX. Its structure was confirmed by the fact that it was converted into Behrend's β -dimethyluracil or 1,4-dimethyl-2,6-dioxypyrimidine,² X., by treatment with hydrochloric acid.



It is interesting to note that methylurea and methylthiourea condense with ethyl cyanacetate to give 2,6-dioxy-3-methyl-4-aminopyrimidine,³ XI., and 2-thio-3-methyl-4-amino-6-oxypyrimidine,⁴ XII., respectively,



It was shown in a previous paper⁵ that pseudoethylthiourea condenses with diethyl formylglycollate to form 2-ethylmercapto-5-ethoxy-6-oxypyrimidine, XIII. We find that ethyl formylphenoxyacetate⁶ also condenses with this pseudothiourea to give 2-ethylmercapto-5-phenoxy-6-oxypyrimidine, XIV.:

¹ Behrend and Thurm: *Loc. cit.*

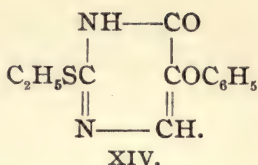
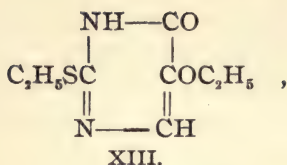
² Behrend and Dietrich: *Loc. cit.* Behrend and Thurm: *Loc. cit.*

³ Conrad: *Ann. Chem. (Liebig)*, **340**, 314.

⁴ Trauber and Winter: *Archiv. Pharm.*, **244**, 11 (1906).

⁵ Johnson and McCollum: *J. Biolog. Chem.*, **1**, 437.

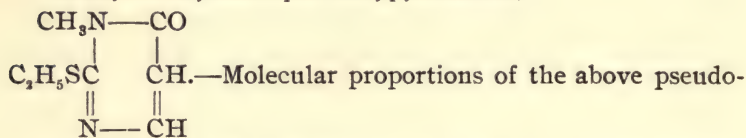
⁶ Johnson and McCollum: *Loc. cit.*



EXPERIMENTAL PART.

Methylpseudoethylthiourea Hydriodide, $\text{CH}_3\text{NHC}(\text{SC}_2\text{H}_5):\text{NH}\cdot\text{HI}$, was prepared by treating monomethylthiourea with ethyl iodide. It was obtained as a heavy oil, which finally solidified in a vacuum over sulphuric acid. The salt was extremely hygroscopic and on prolonged exposure to the atmosphere changed to an oil.

1-Methyl-2-ethylmercapto-6-oxypyrimidine,



urea hydriodide and the sodium salt of ethyl formylacetate were separately dissolved in the least possible quantities of cold water. The 2 solutions were then combined and treated with an aqueous solution containing 1 molecular proportion of potassium hydroxide. The mixture was allowed to stand at ordinary temperatures for about 12 hours and then heated for a few hours on the steam bath. No crystalline material deposited on cooling. The mercaptopyrimidine was extracted with ether and the ether allowed to evaporate spontaneously, when the pyrimidine deposited in prismatic crystals. They were extremely soluble in hot alcohol and in ether, but soluble with difficulty in cold water. The pyrimidine deposited from alcohol in stout prisms, that melted at 79° – 80° , without effervescence, to a clear oil. It was soluble in dilute hydrochloric acid and was precipitated from the acid solution by phosphotungstic acid. Analysis (Kjeldahl):

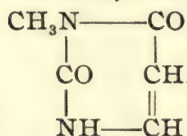
	Calculated for $\text{C}_7\text{H}_{10}\text{ON}_2\text{S}$.	Found.
N	16.47	16.6

The same mercaptomethylpyrimidine was also obtained when 2-ethylmercapto-6-oxypyrimidine¹ was treated with methyl iodide under the following conditions: One molecular proportion of potassium hydroxide and 9.8 grams of 2-ethylmercapto-6-oxypyrimidine were dissolved in 50 cc. of 95 per cent alcohol. Twelve grams of methyl iodide were then added and the solution digested on the steam bath until it gave no alkaline reaction with turmeric. It was then cooled, the insoluble potassium iodide separated by filtration and the excess of alcohol removed by evaporation on the steam bath. We obtained a syrup that would not solidify on cooling. After treatment with a small volume of water, to remove any potassium iodide, the mercaptopyrimidine deposited in well-developed prisms. They were crystallized from alcohol and melted at 79°–80°, to a clear oil. When mixed with the above mercaptopyrimidine the melting point was not changed. Analysis (Kjeldahl):

N	Calculated for C ₇ H ₁₀ ON ₂ S.	Found.	
		I.	II.
	16.47	16.33	16.6

2-Ethylmercapto-6-oxypyrimidine was recovered unaltered after heating with 1 molecular proportion of methyl iodide for 2 hours, at 155°–165°.

1-Methyl-2,6-dioxypyrimidine (1-Methyluracil),



—One and five-tenths grams of 1-methyl-

2-ethylmercapto-6-oxypyrimidine were digested with 15 cc. of 20 per cent hydrochloric acid until the evolution of ethyl mercaptan ceased. When the acid solution was evaporated to dryness the methyluracil deposited in microscopic, prismatic crystals that melted sharply at 174°–175°, without effervescence, to a clear oil. It was extremely soluble in cold water and alcohol but insoluble in benzene. It was not

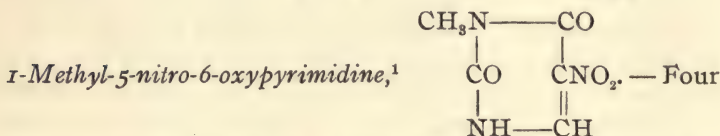
¹ Wheeler and Merriam.

precipitated from its aqueous solution with picric acid. It was dried for analysis at 110° (Kjeldahl):

	Calculated for $C_5H_6O_2N_2$.	Found.
N	22.22	22.21

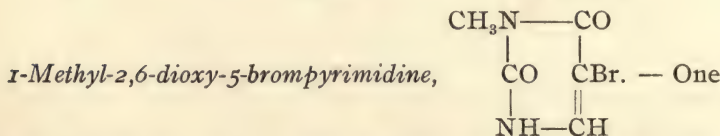
When uracil was heated with 2 molecular proportions of methyl iodide at 186°–200°, for 2 hours, it was recovered unaltered.

	Calculated for $C_4H_4O_2N_2$.	Found.
N	25.0	24.74



and three-tenths grams of 1-methyluracil were dissolved in a mixture of 15 cc. of fuming nitric acid and 15 cc. of concentrated sulphuric acid, and the solution heated on the steam bath until effervescence practically ceased. The acid solution was then poured upon crushed ice, when a heavy, granular precipitate deposited. The compound was soluble with difficulty in cold water, but deposited from hot water in stout, prismatic crystals that melted at 264°–265°, with effervescence, to a clear oil. It deposited from hot alcohol in hexagonal plates. When the compound was mixed with some nitrouracil the melting point was lowered to 240°. It did not contain water of crystallization. Analysis (Kjeldahl):

	Calculated for $C_5H_5O_4N_2$.	Found.
N	24.56	24.8



gram of methyluracil was dissolved in 8 cc. of glacial acetic acid and 1.3 grams of bromine added. Hydrobromic acid was evolved at once and the bromine derivative deposited

¹ Behrend and Thurm: *Loc. cit.*

in prismatic crystals. The compound was soluble in hot water but insoluble in cold. It deposited from 95 per cent alcohol in well-developed, transparent prisms that melted to a clear oil, at 228° – 229° . Analysis (Kjeldahl):

	Calculated for $C_5H_5O_2N_2Br$.	Found.
N	13.65	13.68
$ \begin{array}{c} C_2H_5N \text{---} CO \\ \qquad \qquad \\ CO \qquad \quad CH. \\ \qquad \qquad \\ NH \text{---} CH \end{array} $		
<i>1-Ethyl-2,6-dioxypyrimidine (1-Ethyluracil),</i>		

—This compound was prepared from 2-ethylmercapto-6-oxypyrimidine as follows: The mercaptopyrimidine was first converted into 1-ethyl-2-ethylmercapto-6-oxypyrimidine by treatment with potassium hydroxide and ethyl iodide, as in the preparation of 1-methyl-2-ethylmercapto-6-oxypyrimidine. The diethylmercaptopyrimidine was obtained as an oil, which, without purification, was digested with concentrated hydrochloric acid until the evolution of ethyl mercaptan ceased. When the hydrochloric acid was removed by evaporation the ethyluracil was obtained as a crystalline deposit. The yield was practically quantitative. It was very soluble in hot water and alcohol. It deposited from benzene in foliated prisms that melted at 173° – 174° to a clear oil. Analysis (Kjeldahl):

	Calculated for $C_6H_8O_2N_2$.	Found.
N	20.00	19.75
$ \begin{array}{c} CH_3N \text{---} CO \\ \qquad \qquad \\ CO \qquad \quad CH. \text{ --- This} \\ \qquad \qquad \\ NH \text{---} CCH_3 \end{array} $		
<i>1,4-Dimethyl-2,6-dioxypyrimidine,</i>		

compound has been prepared by Behrend and his co-workers.¹ We obtained it by condensing methylpseudoethylthiourea with ethyl acetoacetate to form 1,4-dimethyl-2-ethylmercapto-pyrimidine. When this mercaptopyrimidine was boiled with concentrated hydrochloric acid the dimethyluracil was formed

¹ *Loc. cit.*

with evolution of ethyl mercaptan. It deposited from hot water in prismatic crystals, that melted at 260° to an oil. The compound agreed in its properties with Behrend's 1,4-dimethyluracil. Analysis (Kjeldahl):

	Calculated for $C_6H_8O_2N_2$.	Found.
N	20.00	20.00

Sodium Salt of Ethyl α -Phenoxy- β -oxyacrylate,
 $NaOCH:C(OC_6H_5)COOC_2H_5$.—Three and two-tenths grams of sodium wire and 1 molecular proportion of absolute alcohol, 6.3 grams, were digested in anhydrous ether until the formation of sodium ethylate was complete. Twenty-five grams of ethyl phenoxyacetate and 10.3 grams of ethyl formate were then added and the ether solution allowed to stand over night, when a colorless, crystalline sodium salt deposited. It was dried in a desiccator over sulphuric acid. Analysis:

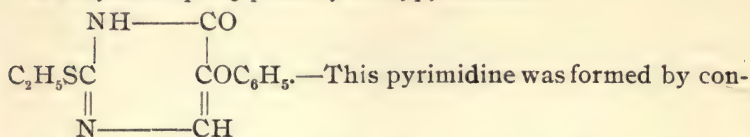
	Calculated for $C_{11}H_{11}O_4Na$.	Found.
Na	10.00	9.65

The free ethyl ester was obtained as a heavy oil when an aqueous solution of the sodium salt was treated with sulphuric acid. It underwent decomposition when we attempted to distil it under diminished pressure.

Hydrazone of Ethyl Formylphenoxyacetate,
 $C_6H_5NHN:CHCH(OC_6H_5)COOC_2H_5$.—Five grams of ethyl formylphenoxyacetate and 3 grams of phenylhydrazine were warmed together in a water-bath, for 30 minutes. They reacted with evolution of heat to form a yellow, crystalline compound. It deposited from warm, 95 per cent alcohol in yellow prisms, that melted at 219° – 221° , with violent effervescence. Analysis (Kjeldahl):

	Calculated for $C_{17}H_{18}O_2N_2$.	Found.
N	9.39	9.3

2-Ethylmercapto-5-phenoxy-6-oxy-4-pyrimidine,



densing pseudoethylthiourea, in aqueous solution, with the sodium salt of ethyl α -phenoxy- β -oxyacrylate. After standing for 6 hours and acidifying with acetic acid, the pyrimidine deposited in prismatic crystals. It crystallized from alcohol in transparent prisms, that melted at 159° to an oil. It responded to a test for sulphur. Analysis (Kjeldahl):

	Calculated for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_2\text{S}$.	Found.
N	11.29	11.06

NEW HAVEN, CONN.,
Feb. 15, 1907.

IV. RESEARCHES ON PYRIMIDINS: ON A COLOR TEST FOR URACIL AND CYTOSIN.

PLATE II.

(Twenty-first Paper.)

BY HENRY L. WHEELER AND TREAT B. JOHNSON.

(*From the Sheffield Laboratory of Yale University.*)

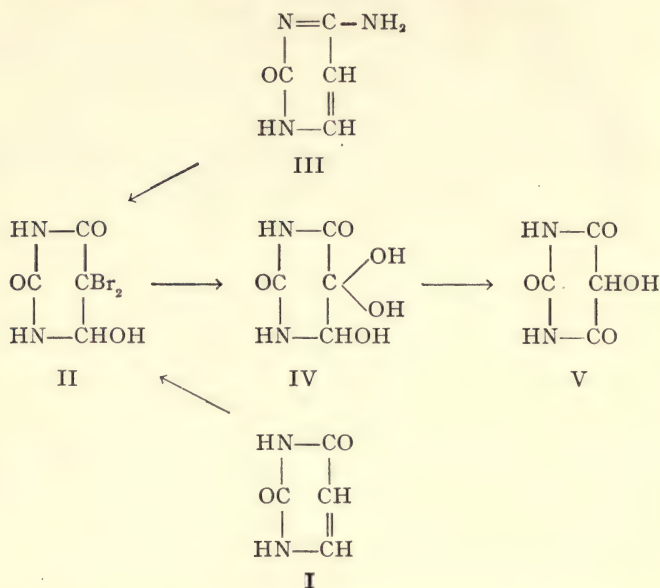
(Received for publication, April 19, 1907.)

When uracil or cytosin is dissolved in bromine water and the solution is treated with an aqueous solution of barium hydroxide in excess, a purple or violet-blue precipitate or color is produced even in dilute solutions.

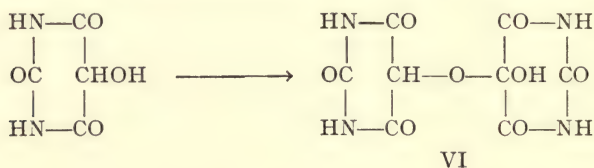
The formation of the purple precipitate involves several intermediate reactions that are explained in the following manner: Uracil (I) and bromine water first react to form dibromoxyhydrouracil (II), and the same compound is also obtained when cytosin (III) is treated with bromine water. Dibromoxyhydrouracil is very sensitive toward alkalies. When treated at ordinary temperature with an excess of barium hydroxide the two atoms of bromine are replaced by hydroxyl groups and isodialuric acid (IV) is formed. Isodialuric acid then undergoes a rearrangement into dialuric acid (V).¹ Both isodialuric and dialuric acids give a violet-blue precipitate with barium hydroxide as observed by Behrend and Roosen.²

¹ Behrend and Köch: *Ann. d. Chem.* (Liebig), cccxv, p. 246, 1901.

² *Ann. d. Chem.*, (Liebig), ccli, p. 244, 1889.



That the present test involves the formation of dialuric acid was shown as follows: The freshly prepared barium precipitate was dissolved in hydrochloric acid and the barium was removed by means of dilute sulphuric acid. On evaporating this solution then in a desiccator we obtained crystals of alloxantin (VI). Dialuric acid undergoes oxidation in the air to alloxantin,¹ while such behavior was never observed in the case of isodialuric acid.²



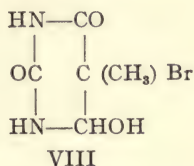
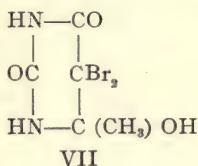
Behrend was the first to show that certain pyrimidins give bromoxyhydro-derivatives. For example, he prepared dibromoxyhydromethyluracil (VII)³ from 4-methyluracil.

¹ Baeyer: *Ann. d. Chem. (Liebig)*, cxxvii, p. 12, 1863.

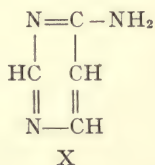
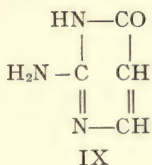
² Behrend and Roosen: *Loc. cit.*

³ *Ann. d. Chem. (Liebig)*, ccxxix, p. 18, 1885.

This compound gives no color with barium hydroxide. Of more interest in connection with the test, however, is the fact that the similar compound from thymine, bromoxyhydrothymine (VIII), described by Walter Jones,¹ also gives no color with barium hydroxide. Obviously these compounds would not be expected to yield dialuric acid on treating with baryta water.



In Richard Burians' interesting work² on the question whether cytosine is a primary product or whether it results by secondary decomposition of some other substance when the nucleic acids are submitted to hydrolysis, he boiled guanine and adenine mixed with various carbohydrates in 30-40 per cent sulphuric acid. He did not obtain cytosine by this treatment, but instead, from guanine 2-amino-6-oxypyrimidine (isocytosine) was formed (IX).³ The synthesis of this pyrimidine has been described by us.⁴ On the other hand, adenine (5 grams) gave 6-aminopyrimidine (X),⁵ (0.5 gram). These pyrimidines are therefore to be considered in the test.



When isocytosine is treated with bromine water it yields a bromine derivative that is not identical with dibromoxyhydrouracil. This substance gives an intense blue color on carefully adding a solution of barium hydroxide. It is a more decided blue

¹ *Zeitschr. f. physiol. Chem.*, xxix, p. 20, 1900.

² *Ergeb. d. Physiol.* (Asher-Spiro), v, p. 794, 1905.

³ *Amer. Chem. Journ.*, xxix, p. 492, 1903.

⁴ Büttner: *Ber. d. deutsch. chem. Gesellsch.*, xxxvi, p. 2232, 1903.

⁵ Wheeler and Bristol: *Amer. Chem. Journ.*, xxxiii, p. 458, 1905.

than that which results from dibromoxyhydrouracil and, what is more important, it is readily distinguished from the latter by immediately disappearing on adding an excess of the barium hydroxide solution. This behavior serves as a delicate test for isocytosin.

Finally 6-aminopyrimidin was prepared by a new method; starting with 2-thiouracil,¹ which can readily be obtained in quantity, 2,6-dichlorpyrimidin was prepared by means of phosphorous pentachloride.² The dichlorpyrimidin then gave 2-chlor-6-aminopyrimidin with alcoholic ammonia, and this was found to reduce smoothly to 6-aminopyrimidin when warmed with concentrated hydriodic acid.

The material thus obtained gave no color whatever with bromine water and barium hydroxide.

THE TEST.

Bromine water is added to about 5 cc. of the solution to be examined until the color is permanent. Too much bromine is to be avoided since a large excess interferes with the test.

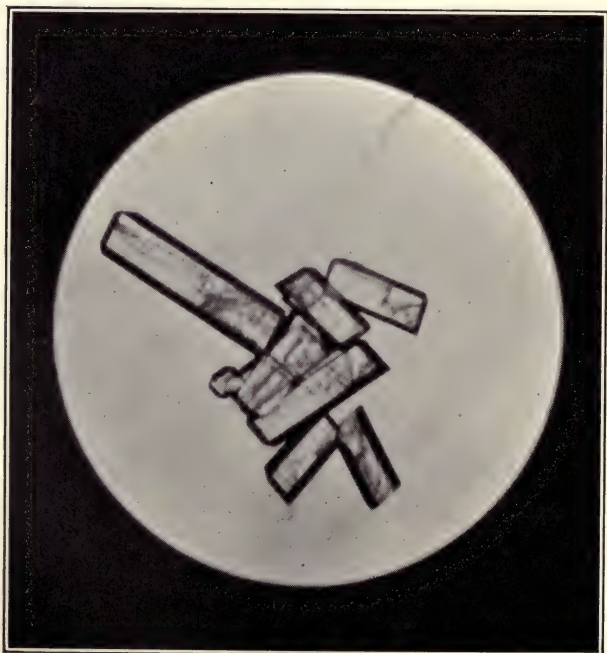
It is advisable, especially when only small quantities of cytosin or uracil are present to remove the excess of bromine by passing a stream of air through the solution. Then on adding barium hydroxide in excess the purple color is almost immediately produced.

Very dilute solutions do not give the test. In such cases on evaporating to dryness and then taking up the material in a little bromine water, removing the excess of bromine, etc., a quantity as small as 0.001 gram of uracil gives a decided bluish-pink or lavender color.

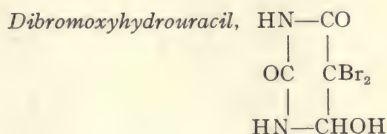
In applying the test in the case of cytosin it is advisable to warm or boil the solution with bromine water, cool, and then apply the test as above, being sure to have a slight excess of bromine present before adding barium hydroxide. Dibromoxyhydrouracil is decomposed by prolonged boiling with water into

¹ Gabriel: *Ber. d. deutsch. chem. Gesellsch.*, xxxviii, p. 1690, 1905; Johnson and Menge: *This Journal*, ii, p. 115, 1906.

² Gabriel: *Ber. d. deutsch. chem. Gesellsch.*, xxxviii, p. 1690, 1905.



5-bromuracil,¹ which gives no color with barium hydroxide. If, however, 5-bromuracil is treated with bromine water it is converted back again into dibromoxyhydrouracil. Picric acid interferes with the color and should be removed before applying the test.



In preparing this compound for use in further experiments we usually took 5 grams of uracil, suspended in 20 cc. of water, and added a little over 15 grams of bromine. The uracil dissolved completely on warming, and, on cooling, a crystalline mass separated. The material thus obtained had a yellow color from excess of bromine, and the yield that first separated was almost 90 per cent of the calculated. On crystallizing once from water colorless, large, flat prisms or blocks separated. The habit of these crystals is shown in the microphotographs (magnified 60 times) Plate II.

The same substance was obtained when 0.6 gram of cytosin sulphate was suspended in water and bromine added until the salt dissolved. The solution was then concentrated to a small volume and cooled. The prisms obtained melted at 205–6° C. (Analysis (III)).

The analytical results were as follows:

	Calculated for $\text{C}_4\text{H}_4\text{O}_3\text{N}_2\text{Br}_2$:	I.	II.	Found:	III.	IV.
N.....	9.72	9.59	9.63	9.46		
Br.....	55.55					56.00

Dibromoxyhydrouracil melts with effervescence at 203–6°. It shows signs of decomposition below this temperature. It is more soluble in water than uracil. The solution of the pure white crystals is neutral to litmus, but on boiling it has an acid reaction and finally 5-bromuracil separates. In accordance with this silver nitrate gives no precipitate in the cold but on warming with this reagent silver bromide separates.

¹ Wheeler and Merriam: *Amer. Chem. Journ.*, xxix, p. 486, 1903.

Dibromoxyhydrouracil dissolves readily in alcohol. If boiled with alcohol 5-bromuracil separates. If the alcoholic solution is treated with a solution of sodium in alcohol a purple precipitate is at once produced similar to the barium hydroxide precipitate. Alcoholic potassium hydroxide also produces a similar colored precipitate. These colored alkali salts differ from the barium hydroxide precipitate by being instantly decomposed and decolorized by treatment with water. The aqueous solution then turns green and finally orange on standing.

Aqueous ammonia immediately dissolves the dibrom-derivative, and removes bromine; the solution slowly takes on yellow, then a garnet color and if sufficient material is present a reddish-brown precipitate separates.

Dibromoxyhydrouracil is almost insoluble in ether.

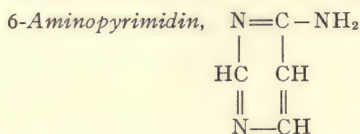
THE PURPLE PRECIPITATE.

The precipitate produced by adding barium hydroxide to an aqueous solution of dibromoxyhydrouracil when exposed on paper to dry in the air turned red. When treated with acetic acid it changed to a bright red powder, while the precipitate when freshly precipitated dissolved completely in acetic acid. The analysis of the precipitate was therefore abandoned. It was shown that the substance yields alloxantin on treatment with acids as follows: Four and a half grams of dibromoxyhydrouracil were dissolved in 40 cc. of water and added to 11 grams of crystallized barium hydroxide in 100 cc. of water. The purple precipitate was rapidly filtered but no attempt was made to wash it. It was immediately dissolved in dilute hydrochloric acid and the barium was removed by adding 20 per cent of sulphuric acid. The colorless solution, which on testing a portion with barium hydroxide again gave a purple precipitate, was allowed to evaporate in a desiccator. On standing over night it gave small, stout, colorless transparent prisms. These melted at 243° C. with effervescence. Behrend and Friedrich¹ state that alloxantin melts at $243-5^{\circ}$. This material was not dialuric acid since its aqueous solution failed to decompose carbonate of sodium and it was not

¹ *Ann. d. Chem.* (Liebig), cccxlv, p. 11, 1906.

isodialuric acid because it melted over 100° higher. A nitrogen determination agreed with the calculated for alloxantin:

	Calculated for $C_8H_6O_8N_4 + 2H_2O$:	Found:
N.....	17.40 per cent.	17.11 per cent.



One gram of 2-chlor-6-aminopyrimidin was dissolved in 20 cc. of colorless, concentrated hydriodic acid and then evaporated to dryness on the water bath. Iodine separated in abundance. The residue was evaporated several times with a solution of sulphur dioxide. The colorless solution was then treated with an excess of silver sulphate, filtered and the silver was then removed with hydrogen sulphide. On concentrating the solution a syrup was obtained, which, when taken up in boiling alcohol, gave well-crystallized colorless prisms. The yield was over 0.8 gram. The crystals melted at 143° to clear oil, and nitrogen determinations agreed with the calculated for an acid sulphate of 6-aminopyrimidin.

	Calculated for $C_4H_6N_3.H_2SO_4$:	I.	Found:	II.
N.....	21.76	21.55		21.11

The solution of this material was freed from sulphuric acid by means of barium hydroxide and the excess of barium hydroxide was removed with carbonic acid. The free base proved to be extremely soluble in water. The aqueous solution was precipitated by phosphotungstic and picric acid, and it gave a precipitate of silver salt when treated with silver nitrate in neutral solution. This precipitate was soluble in ammonia. With bromine water and barium hydroxide it gave no color.

V. RESEARCHES ON PYRIMIDINS: ON SOME SALTS OF CYTOSIN, ISOCYTOSIN, 6-AMINOPYRIMIDIN AND 6-OXYPYRIMIDIN.

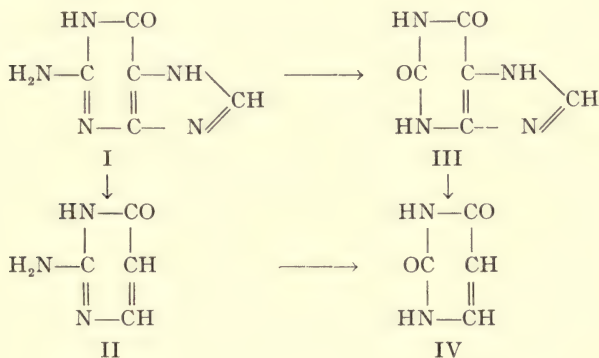
(Twenty-second Paper.)

By HENRY L. WHEELER.

(From the Sheffield Laboratory of Yale University.)

(Received for publication, June 10, 1907.)

It has been shown by Richard Burian¹ when guanin (I), mixed with carbohydrates, is heated with 30-40 per cent sulphuric acid that hydrolysis and reduction take place at the same time, the imidazole group is removed and isocytosin² (II) and uracil (IV) result. It may be added that the probable formation and decomposition of xanthin (III) would also give uracil. This decomposition of guanin may be represented as follows:

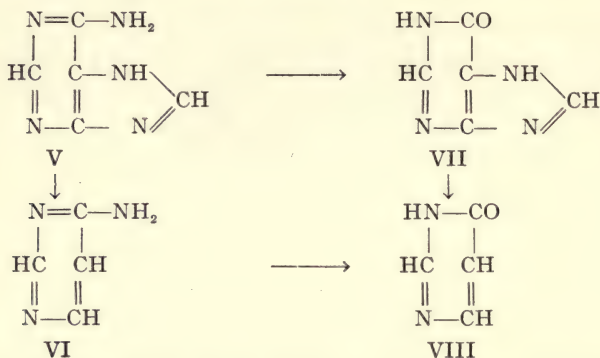


When adenin (V) was treated in a similar manner, Burian obtained 6-aminopyrimidin (VI), while 6-oxypyrimidin (VIII), which would be expected to result in this case both by the

¹ Asher-Spiro: *Ergeb. d. Physiol.*, v, p. 795, 1905.

² Wheeler and Johnson: *Amer. Chem. Journ.*, xxix, p. 492, 1903.

decomposition of hypoxanthin (VII) and by the hydrolysis of 6-aminopyrimidin, escaped detection.¹



The three pyrimidin bases, isocytosin, 6-aminopyrimidin and 6-oxypyrimidin, are probably formed in the energetic hydrolysis of the nucleic acids by sulphuric acid and, since it has now been found that the general reagents which precipitate cytosin also precipitate these bases, an examination of the properties of the compounds and some of their salts was undertaken, along with the similar ones of cytosin. The statement of Burian that 6-aminopyrimidin and isocytosin according to their entire behavior must obstinately adhere to cytosin ("dem sie ihrem ganzen Verhalten nach hartnäckig anhaften müssten") has been found to be more especially true in the case of isocytosin.

Of the three bases 6-oxypyrimidin is new. Isocytosin was first prepared synthetically in this laboratory² and later it was obtained in a different manner by Gabriel and Colman.³

In the case of 6-aminopyrimidin, Burian states that the base was isolated in the form of the silver salt, by precipitating in neutral solution with silver nitrate. This was decomposed by means of hydrogen sulphide and the base precipitated by phosphotungstic acid. A solution of the free base was then obtained in the usual manner from which he prepared and analyzed the

¹ In an article published while this paper was in press (*Zeitschr. f. physiol. Chem.*, li, p. 444, 1907), Burian describes the isolation of 6-oxypyrimidin.

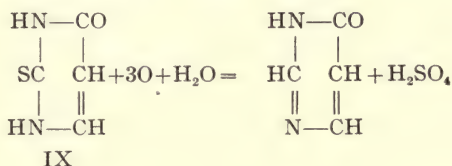
² *Loc. cit.*

³ *Ber. d. deutsch. chem. Gesellsch.*, xxxvi, p. 3382, 1903.

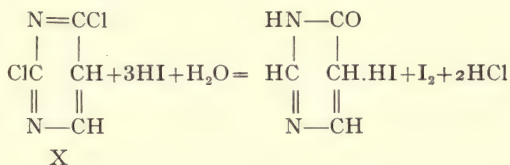
picrate and chloroplatinate. He says nothing further in regard to the base or its salts.

6-Aminopyrimidin, however, was first prepared by Ernst Büttner, who obtained it from barbituric acid by means of a series of operations.¹ This author described the free base and he prepared the hydrochloride, easily soluble rhombic tables; the chloroplatinate and picrate, needles, difficultly soluble. Our knowledge of these pyrimidins stood at this point when the following work was begun.

It has now been found that 6-oxypyrimidin is formed when 2-thiouracil (IX), which can be easily prepared² in any desired quantity, is treated with hydrogen dioxide.



The writer finds, however, that 6-oxypyrimidin is more smoothly obtained by warming 2, 6-dichlorpyrimidin (X), prepared from uracil³ or 2-thiouracil,⁴ with hydriodic acid and red phosphorus. The hydrogen iodide salt results from which the pure base can be obtained in the usual manner.



The 6-aminopyrimidin used in this work was prepared by a shorter and more convenient method than the one employed by Büttner mentioned above. 2, 6-Dichlorpyrimidin⁵ was heated

¹ *Ber. d. deutsch. chem. Gesellschaft.*, xxxvi, p. 2232, 1903.

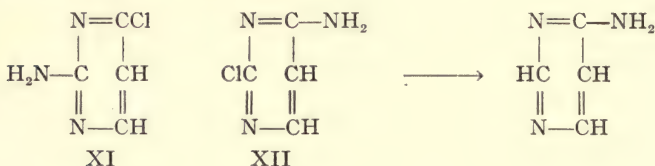
² Wheeler and Bristol: *Amer. Chem. Journ.*, xxxiii, p. 458, 1905.

³ Gabriel: *Ber. d. deutsch. chem. Gesellschaft.*, xxxviii, p. 1690, 1905.

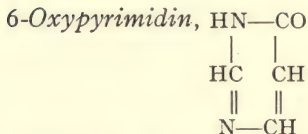
⁴ Johnson and Menge: *This Journal*, ii, p. 114, 1906.

⁵ Care should be taken in working with 2, 6-dichlorpyrimidin not to expose the material to the skin, since it has a very corrosive action. In one case deep and painful blisters were formed on the hands, resembling those produced by hydrofluoric acid.

with alcoholic ammonia. This gave a mixture of 2-amino-6-chlorpyrimidin (XI) and 2-chlor-6-aminopyrimidin (XII).¹ It was found, on boiling this mixture with water and zinc dust, that 2-amino-6-chlorpyrimidin was reduced to the very soluble 2-aminopyrimidin² which could easily be removed, while 2-chlor-6-aminopyrimidin remained unaltered. The pure 2-chlor-6-aminopyrimidin then on warming on the steam-bath with hydriodic acid was smoothly reduced and the hydrogen iodide salt of 6-aminopyrimidin was obtained. Although Büttner worked with small quantities of this base (0.25 gram) his results and the writer's agree in every respect.



EXPERIMENTAL PART.



Thirteen grams of 2,6-dichlorpyrimidin were slowly added to 50 cc. of concentrated hydriodic acid and 6 grams of red phosphorus on the steam-bath. As soon as all was added the mixture was boiled for a few minutes and then the hydrogen iodide was removed, as far as possible, by evaporation in a vacuum at 100°. The residue on taking up in hot water and filtering from red phosphorus formed a syrup, which deposited well crystallized needles, decomposing with effervescence when kept at 300° (6-oxypyrimidin hydriodide). The whole was dissolved in water and an excess of silver sulphate was added and filtered, the filtrate was precipitated with hydrogen sulphide, the phosphoric and sulphuric acids removed by means of barium

¹ Gabriel: *Loc. cit.*

² Büttner: *Loc. cit.*

hydroxide, and then, on removing the excess of barium with carbon dioxide and evaporating to dryness, a very soluble crystalline cake was obtained. This weighed 5.6 grams. On crystallizing from ethyl acetate beautiful, long, thin, prismatic needles separated melting to a clear oil at 164° – 165° . The per cent of nitrogen in this material agreed with the calculated for 6-oxypyrimidin (Analysis I and II).

The same compound was also obtained as follows: Twenty grams of 2-thiouracil were suspended in a liter of hot water and about 530 cc. of commercial hydrogen dioxide solution were added in portions. The thiouracil dissolved and after boiling a few minutes, sulphur dioxide was added and the solution was evaporated to a convenient volume. The sulphuric acid, which had been formed in the reaction, was removed by means of an excess of barium hydroxide and the excess of the latter was precipitated with carbon dioxide. The solution was then evaporated to dryness and the residue was extracted with boiling alcohol. This dissolved the 6-oxypyrimidin, leaving a mixture weighing about 7.7 grams of uracil and a barium salt of an organic acid that was not further examined. The barium salt was insoluble in alcohol but readily soluble in water, it had the peculiar property of swelling up to many times its original volume when heated on platinum foil.

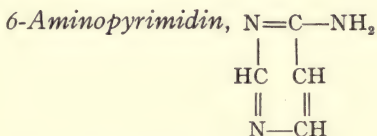
The alcoholic solution was evaporated to dryness and the residue extracted with ethyl acetate. This gave about 6 grams of crude 6-oxypyrimidin. When crystallized from a large amount of benzene it formed colorless needles melting less sharply than the above preparation (Analysis III). All the nitrogen determinations in this paper were made by Kjeldahl's method.

	Calculated for $C_4H_4ON_2$:	I.	Found: II.	III.
N	29.16	29.02	28.78	28.85

6-Oxypyrimidin is insoluble in petroleum ether, very difficultly soluble in ether, somewhat more soluble in hot benzene and still more soluble in ethyl acetate. This solvent is the best to use to extract and crystallize the material. It is extremely soluble in water and alcohol, and, in this respect, like 6-aminopyrimidin could not possibly be mistaken for the far more insoluble cytosin and isocytosin.

This monoöxypyrimidin unlike the dioxypyrimidin (uracil) gives no color with bromine and barium hydroxide.

It is precipitated by phosphotungstic acid, and, in neutral solution, by silver nitrate or mercuric chloride. A strong solution is precipitated by picric acid and also by hydrochloro-platinic acid. The platinum chloride double salt separates slowly and forms prisms. It did not have a definite melting or decomposing point.



2-Chlor-6-aminopyrimidin reduces smoothly to 6-aminopyrimidin when warmed on the water-bath with concentrated hydriodic acid and red phosphorous.¹ The residue, after the removal of hydrogen iodide by evaporation was treated with silver sulphate, barium hydroxide, etc., as in the case of 6-oxypyrimidin, for the preparation of the free base. It was found that 2.7 grams of 2-chlor-6-aminopyrimidin, 27 cc. of concentrated hydriodic acid and an excess of red phosphorus gave 1.6 gram of crude base while the calculated is 1.9 gram. When crystallized from ethyl acetate, snow white clusters of thin, leaf-like crystals separated. The appearance of these clusters was similar to those of 6-oxypyrimidin. The material melted at 151°–152°. Büttner² gives the same melting point for this base. It is extremely soluble in water and alcohol and it is precipitated in more dilute solutions by the same reagents which precipitate 6-oxypyrimidin.

The Acetyl Compounds.

A peculiar acetyl derivative of 6-oxypyrimidin was formed when the base was dissolved in acetic anhydride and evaporated to dryness on the steam-bath. When the residue was crystallized from alcohol, in which it is quite soluble, it formed colorless needles or spikes. It is sharply distinguished from the other

¹ Wheeler and Johnson: *This Journal*, iii, p. 186, 1907.

² *Loc. cit.*

acetyl compounds by having two melting points. When heated rapidly it melted to a clear oil at 180° , or a little below, then if the temperature was kept at this point it solidified and on further heating it remelted with effervescence at 215° – 220° . (Analysis I and II.)

Another sample of the acetyl compound was prepared and crystallized from water. It then separated in the form of prismatic scales which had the same behavior on heating as the above. It was dried at 50° – 55° .

(Analysis III.) The analytical results are low for a simple acetyl derivative, but they agree with the calculated for the expected acetyl compound with a molecule of water of crystallization, or, if water of constitution, equally well for acetylformamidine acrylic acid, $\text{CH}_3\text{CONH}-\text{CH}=\text{N}-\text{CH}=\text{CHCOOH}$, or simply an acetic acid salt of 6-oxypyrimidin. The latter, however, is excluded since the free base dissolves in glacial acetic acid and on evaporation is recovered unaltered.

In order to determine whether the compound has water of crystallization or water of constitution, a portion of the material, which had been crystallized from water, was heated at 109° – 115° for three hours. It then lost 4 per cent in weight. This was due, not to the fact that water was given off but that the substance volatilized, since a nitrogen determination, after heating, gave the same result as in the case of the previous determinations (Analysis IV). This result makes it appear improbable that the substance has water of crystallization. The view that the compound is acetylformamidine acrylic acid, therefore, remains at present as most probable. This, however, must be left for future work to decide.

	Calculated for $\text{C}_6\text{H}_5\text{O}_3\text{N}_2$:	I.	II.	Found: III.	IV.
N	17.94	17.75	17.64	17.88	17.86

Acetyl-6-aminopyrimidin.—A quarter of a gram of the pure base was dissolved in acetic anhydride and heated to boiling, then evaporated to dryness on the steam-bath. When crystallized from about 5 cc. of water it formed an asbestos-like mass of fine needles. About 0.2 gram separated. It melted at 202° , to a clear oil, without effervescence. Analysis:

	Calculated for $\text{C}_6\text{H}_7\text{ON}_3$:	Found:
N	30.43	30.35

The Picrates.

The picrate of 6-oxypyrimidin is far more soluble than the picrates of cytosin and isocytosin. It also differs decidedly in appearance from these salts. 6-Aminopyrimidin picrate, on the other hand, closely resembles cytosin picrate both in regard to solubility and crystalline form. The presence of this picrate is possibly the cause of the picrate of cytosin from natural sources invariably melting lower than that of synthetic cytosin.¹

6-Oxypyrimidin Picrate.—A saturated aqueous solution of picric acid was mixed with a moderately strong solution of 6-oxypyrimidin; as no precipitate was formed the solution was concentrated to almost the volume of picric acid solution employed. On standing a long, flat, fern-like growth of crystals separated. It melted to a clear oil at 190°. Analysis:

	Calculated for $C_{10}H_7O_8N_5$:	Found:
N	21.53	21.55

6-Aminopyrimidin Picrate.—Forty cc. of picric acid solution were added to 0.2 gram of 6-aminopyrimidin in a little water. A bulky precipitate was formed at once which dissolved on adding 40 cc. of water and then boiling. On cooling, long bright, yellow, hair-like needles separated. On heating these showed evidence of change a little below 200° and then suddenly melted at 226° to a clear oil. This then turned brown and vigorously effervesced at 270°–280°. Analysis:

	Calculated for $C_{10}H_8O_7N_6$:	I.	Found:	II.
N	25.92	25.76		25.92

The Hydrochlorides.

The hydrochlorides of 6-oxypyrimidin, 6-aminopyrimidin and of isocytosin are even more soluble than the easily soluble cytosin hydrochloride. The latter and 6-oxypyrimidin hydrochloride separate with water of crystallization. The hydrochlorides are difficultly soluble in alcohol.

6-Oxypyrimidin Hydrochloride, $C_4H_4ON_2 \cdot HCl \cdot H_2O$.—Pure 6-oxypyrimidin was dissolved in dilute hydrochloric acid and evaporated to dryness on the steam-bath. The residue formed a syrup

¹ *Amer. Chem. Journ.*, xxix, pp. 494, 500, 505, 1903.

which solidified on cooling. It was dissolved in water and allowed to crystallize by standing over sulphuric acid. Thick transparent prisms or oblong blocks separated some 10–15 millimeters in length. These melted partially below 100° , finally melting to an oil at about 205° – 210° . Analysis:

	Calculated for $C_4H_7O_2N_2Cl$:	I.	Found: II.
N	18.60	18.54	18.64

A water determination was made by heating the material at 114° for one hour. This gave 13.1 per cent while the calculated is 11.96. When reheated at 120° it was found that the material slowly volatilized, which explains the high result.

6-Aminopyrimidin Hydrochloride, $C_4H_5N_3.HCl$.—The base was evaporated to dryness with hydrochloric acid. The material was then taken up in a little water and left to crystallize in a desiccator. Transparent prisms or tables separated from the syrupy solution. When dried over calcium chloride they melted to an oil at 257° and then effervesced. A nitrogen determination showed that the salt was anhydrous.

	Calculated for $C_4H_5N_3.HCl$:	Found:
N	31.93	31.49

Isocytosin Hydrochloride, $C_4H_5ON_3.HCl$.—This salt has a decided tendency to crawl up the sides of a dish when left to crystallize. The crystals which separate in this manner are prisms, when precipitated from an aqueous solution by the addition of alcohol it forms little square tables or blocks. When heated it begins to change in appearance at about 250° and then effervesces about 270° . Analysis:

	Calculated for $C_4H_5ON_3.HCl$:	Found:
N	28.47	28.27

Cytosin Hydrochloride, $C_4H_5ON_3.HCl.H_2O$.—If cytosin is dissolved in strong hydrochloric acid and left to crystallize in a desiccator cytosin dihydrochloride is obtained, $C_4H_5CN_3_2HCl$.¹ If the acid solution is evaporated to dryness and the residue is taken up in water and left to crystallize spontaneously, large, transparent plates separate of the hydrous, 1:1 salt. This salt

¹ Wheeler and Johnson: *Amer. Chem. Journ.*, xxxi, p. 598, 1904.

loses its water rapidly at 50° and in a few hours on exposure to the air. It differs from the hydrous 6-oxypyrimidin hydrochloride since on standing over night the crystals become entirely opaque. It is more soluble than the dihydrochloride. The latter and also the hydrous cytosin hydrochloride both melt at 275° – 279° . Analysis:

	Calculated for $C_4H_5ON_3.HCl.H_2O$:	Found:
N	25.37	25.52

Some of the material which had stood for about 3–4 hours was dried to a constant weight at a little above 100° . It lost 9.5 per cent of water while the calculated for one molecule of water is 10.8 per cent.

The Sulphates.

The sulphates of 6-oxypyrimidin and 6-aminopyrimidin are very soluble in water. The neutral sulphate of isocytosin is less soluble and it resembles the neutral sulphate of cytosin except that it does not crystallize with water. The three sulphates which cytosin forms have been prepared and some new facts are given for their identification. The sulphates were prepared from the hydrochlorides by treating the latter with an excess of silver sulphate, removing the excess of silver by means of hydrogen sulphide and then evaporating. Owing to their solubility, the sulphates of 6-oxypyrimidin and 6-aminopyrimidin were crystallized by means of alcohol. The sulphates of isocytosin and cytosin were allowed to crystallize at ordinary temperatures in order to determine their degree of hydration.

6-Oxypyrimidin Sulphate, $(C_4H_4ON_2)_2H_2SO_4$.—This salt was purified by precipitating the strong aqueous solution with alcohol. After the fourth precipitation it came down in the form of microscopic prisms and melted with effervescence about 218° . Analysis:

	Calculated for $C_8H_8O_2N_4.H_2SO_4$:	I.	Found:	II.
N	19.31	19.29		19.32

This neutral sulphate also separates from alcoholic solutions containing a considerable excess of sulphuric acid.

6-Aminopyrimidin Sulphate, $C_4H_5N_3.H_2SO_4$, was described in a previous paper.¹

Isocytosin Sulphate, $(C_4H_5ON_3)_2.H_2SO_4$.—This salt separated from the aqueous solution containing a slight excess of sulphuric acid, on standing, in the form of balls composed of radiating clusters of small prisms. It melted at 276° with effervescence. Analysis:

	Calculated for $C_8H_{10}O_2N_6.H_2SO_4$:	I.	Found:	II.
N.....	26.25	26.30		25.98

Basic Cytosin Sulphate, $(C_4H_5ON_3)_4.H_2SO_4.2H_2O$.—This hydrous salt has frequently been obtained by Levene.² It was obtained in the anhydrous condition by Kossel and Steudel.³ It is the least soluble of the sulphates mentioned in this paper. It has the highest decomposing point, the same as that of cytosin itself, namely, 323° . It was obtained, in the present work, when cytosin monohydrochloride was treated with a slight excess of silver sulphate, and the silver then removed by means of hydrogen sulphide. On concentrating the solution the salt separated in the form of sharply defined, long, needle-like prisms.

Neutral Cytosin Sulphate, $(C_4H_5ON_3)_2.H_2SO_4.2H_2O$.—The anhydrous form of this salt was first obtained by Levene,⁴ having dried the material in a toluol bath. The hydrous form, here described, separated on allowing the mother liquor from the above basic salt to evaporate in the air. Stouter, more compact masses of prisms formed which, on drying in the air, melted with effervescence at 287° . Levene found 290° . The analyses now show that this salt crystallizes with two molecules of water.

	Calculated for $C_8H_{10}O_2N_3.H_2SO_4.2H_2O$:	I.	Found:	III.
N.....	23.59	23.66	23.45	
H ₂ O	10.11			10.13

The water determination was made by heating the salt at 118° – 120° for an hour.

Acid Cytosin Sulphate, $C_4H_5ON_3.H_2SO_4$.—This salt has been obtained by Kossel and Steudel; they simply mention that it is

¹ Wheeler and Johnson: This *Journal*, iii, p. 189, 1907.

² *Zeitschr. f. physiol. Chem.*, xxxix, pp. 7, 135, 481, 1903.

³ *Ibid.*, xxxviii, p. 52, 1903.

⁴ *Ibid.*, xxxviii, p. 81, 1903.

easily soluble.¹ It is easily obtained by dissolving the neutral sulphate in 20 per cent sulphuric acid and allowing the material to crystallize in a desiccator. The stout, transparent crystals thus obtained appear to be rhombohedral. These have the characteristic property of becoming opaque when an attempt is made to wash them with water. This is the most soluble sulphate of cytosin. After pressing on paper and drying over calcium chloride the material melted at 197° to a colorless oil. Analysis:

	Calculated for $C_4H_5ON_3.H_2SO_4$:	I.	Found: II.
N	20.09	19.86	19.89

Acid Cytosin Phosphate, $C_4H_5ON_3.H_3PO_4$.—This salt was obtained when cytosin monohydrochloride (7 grams) was boiled with phosphorous oxychloride (50 cc.) for two hours. The phosphorous oxychloride was then evaporated and the residue treated with ice. The material dissolved and, evaporating, a syrup was obtained from which dilute alcohol precipitated well crystallized, long, flat prisms. When crystallized from water, in which the salt is very soluble, it melted at 236° with effervescence. Analysis:

	Calculated for $C_4H_5ON_3.H_3PO_4$:	I.	Found: II.
N	20.09	20.09	19.95

The melting or effervescing points of the substances compared in this work are given in the following table. The effervescing points even of the pure compounds may vary to a certain amount, perhaps several degrees, according to the rate of heating, amount of substance used, etc. No especial accuracy is claimed. It is believed, however, that the melting points given will be found to be sufficiently constant to serve as an aid for the identification of the substances. There is in general a wide difference in the melting points in each series. This should be especially serviceable in the case of the sulphates of cytosin.

The picrolonates mentioned in the table are the most insoluble salts prepared. Since some new facts have been observed in the case of picrolonates these salts will be described in a later paper.

¹ *Zeitschr. f. physiol. Chem.*, xxxviii, p. 52, 1903.

Base	Acetyl Derivative	HCl Salts	H ₂ SO ₄ Salts	Picrate	Picrolonate
$\begin{array}{c} \text{HN}-\text{CO} \\ \\ \text{HC}-\text{CH} \\ \\ \text{N}-\text{CH} \\ \text{6-oxyypyrimidin} \end{array}$	180°* 215°	C ₄ H ₄ ON ₂ .HCl.H ₂ O* 205°-210°	(C ₄ H ₄ ON ₂) ₂ H ₂ SO ₄ * 218°	190°*	193°
$\begin{array}{c} \text{N}=\text{C}-\text{NH}_2 \\ \\ \text{HC}-\text{CH} \\ \\ \text{N}-\text{CH} \\ \text{6-aminopyrimidin} \end{array}$	202°*	C ₄ H ₃ N ₃ .HCl* 257°	C ₄ H ₃ N ₃ .H ₂ SO ₄ ** 143°	226°*	261°
$\begin{array}{c} \text{HN}-\text{CO} \\ \\ \text{H}_2\text{N}-\text{C}-\text{CH} \\ \\ \text{CH} \\ \text{isocytosin} \end{array}$	247°†††	C ₄ H ₃ ON ₃ .HCl* 270°	(C ₄ H ₃ ON ₃) ₂ H ₂ SO ₄ * 276°	270°-280°†	273°-275°
$\begin{array}{c} \text{N}=\text{C}-\text{NH}_2 \\ \\ \text{OC}-\text{CH} \\ \\ \text{HN}-\text{CH} \\ \text{cytosin} \end{array}$	Above 300°†	C ₄ H ₆ ON ₃ .2HCl† 275°-279° C ₄ H ₆ ON ₃ .HCl.H ₂ O* 275°-279°	C ₄ H ₃ ON ₃ .H ₂ SO ₄ * 197° (C ₄ H ₃ ON ₃) ₂ H ₂ SO ₄ .2H ₂ O* 287°-290° †† (C ₄ H ₃ ON ₃) ₄ H ₂ SO ₄ .2H ₂ O* 323°	Above 300°†	270°

* This paper. † Wheeler and Johnson: *Amer. Chem. Journ.*, xxix, p. 492, 1903. ‡ *Ibid.*, xxxi, p. 598, 1904.

** This *Journal*, iii, p. 183, 1907. †† Levene: *Zeitschr. f. physiol. Chem.*, xxxviii, p. 81, 1903.

‡‡ Gabriel and Colman: *Ber. d. deutsch. chem. Gesellschaft.*, xxxvi, p. 3382, 1903.

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September, 1907.]

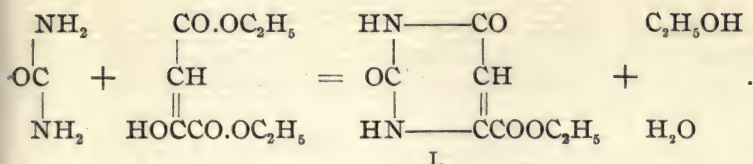
CXLVI.—RESEARCHES ON PYRIMIDINES: URACIL
4-CARBOXYLIC ACID.

[TWENTY-THIRD PAPER.]

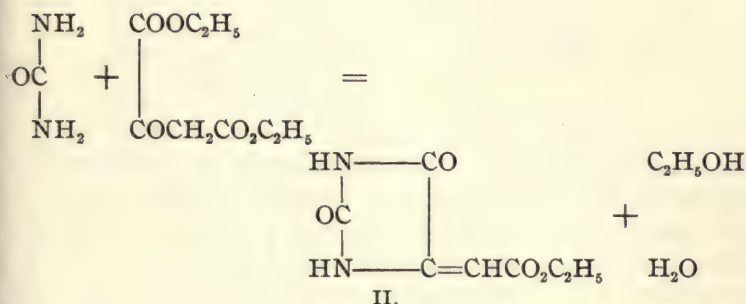
BY HENRY L. WHEELER.

In 1897, Müller¹ described a substance obtained by condensing oxalaceticethyl ester with urea by means of hydrogen chloride in glacial acetic acid. His analytical results showed that the condensation involved the separation of water and alcohol, and he represented the reaction as taking place with the formation of uracil-4-ethylcarboxylate as follows:

¹ J. prakt. Chem., 56, 488 (1897).

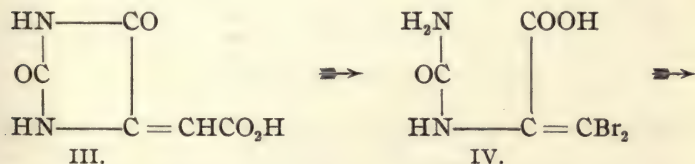


There is nothing in Müller's article, however, to show that the product formed was a pyrimidine. The condensation might result with the separation of water and alcohol from the oxalyl radical; the process would then be represented as follows:

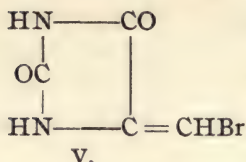


An acid called pyvureidic acid (Pyvureidsäure), corresponding to this ester, has been recently described by Gabriel,¹ who obtained it by treating malyureidic acid with bromine.

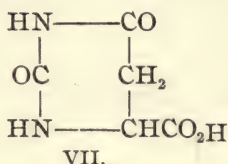
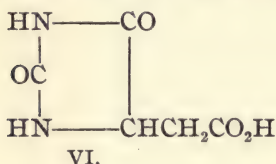
Formula III. has been assigned by Gabriel to pyvureidic acid since with bromine water it yields dibrompyvurinic acid, IV., the same substance also being obtained in a similar manner from brompyvureid, V.



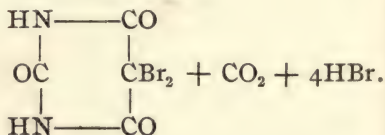
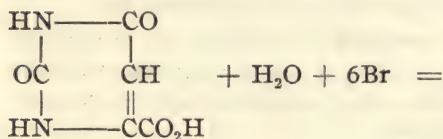
¹ Ann. Chem. (Liebig), **348**, 89 (1906).



Since pyvureïdic acid is to be represented by formula III., then malyureïdic acid has the five-membered ring structure, VI., given to it by Guareschi¹ and not that of a dihydrouracil-carboxylic acid, VII., as represented by Grimaux.²



The writer has prepared Müller's ester and finds, on saponification, that it gives an acid isomeric, and not identical, with Gabriel's pyvureïdic acid. The action of bromine water on this acid shows that the substance is a pyrimidine. This was tried, following the directions given by Gabriel in the case of pyvureïdic acid. The acid dissolved, carbon dioxide was evolved and, on evaporating the solution, large crystals of dibrombarbituric acid separated. The reaction can be represented as follows:



This proves that the acid in question is uracil-4-carboxylic

¹ Ber. d. chem. Ges., **10**, 1748 (1877).

² Jahres. d. Chem., 1876, p. 752. Ann. chim. phys. [5], **11**, 413 (1877). Bull. Soc. Chim. [2], **24**, 337 (1875).

acid and that Müller's ester has the pyrimidine structure, I., originally assigned to it. It also confirms Gabriel's conclusions that pyvureïdic and malyureïdic acids are not pyrimidines.

Uracil-4-carboxylic acid has its carboxyl group much more firmly bound than the isomeric uracil-5-carboxylic acid. It is not converted into uracil when heated with 20 per cent sulphuric acid at 200° , while the isomeric 5-derivative readily yields uracil on heating with acids.¹ This excludes the possibility that uracil exists in the nucleic acids as a 4-carboxyl derivative. Unlike the isomeric pyvureïdic acid, uracil-4-carboxylic acid crystallizes with 1 molecule of water of crystallization. The hydrous acid has the empirical formula of orotic acid, but its melting point is different. The melting point of its methyl and ethyl esters also differ from those of the corresponding esters of orotic acid.

The yield of uracil-4-ethylcarboxylate, by Müller's method, is only about 20 per cent of the calculated, and attempts were made to prepare it by treating ethylpseudothiurea hydrobromide in alkaline solution with oxalaceticethyl ester. This gave no pyrimidine, but instead a pseudourea addition product or salt. Owing to the poor yield of this product, no attempt was made to convert it into the pyrimidine by heating, as has been found to prove successful by Gabriel and Colman in the case of the analogous addition product of anisamidine and acetylacetone.² In this connection, and in regard to the limits of our general method for the preparation of pyrimidines, it is interesting to note that such acid molecules as acetylethylcyanacetate, $\text{CH}_3\text{COCH}(\text{CN})\text{CO}_2\text{C}_2\text{H}_5$, and oxal-malonic ethyl ester, $\text{C}_2\text{H}_5\text{OCOCOCH}(\text{CO}_2\text{C}_2\text{H}_5)_2$, also failed to condense with the pseudourea, but like oxalacetic ethyl ester, formed addition products. On the other hand, Dr. Johnson has found that oxalpropionic ester,



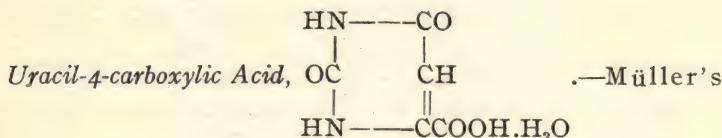
condenses normally in alkaline solution, giving 2-mercapto-4-carbethoxy-5-methyl-6-oxypyrimidine.

¹ THIS JOURNAL, **37**, 392 (1907).

² Ber. d. chem. Ges., **32**, 1529 (1899).

Ruhemann and Stapleton¹ found that ethyl acetylenedicarboxylate, $C_2H_5OCOC\equiv CCOOC_2H_5$, condenses with guanidine to form 2-amino-6-oxy-4-ethylcarboxylate; whether uracil-4-carboxylic acid can be prepared more readily from this substance than by the above method, or, by the condensation of the acetylene ester with a urea derivative, must be left for future work to decide.

EXPERIMENTAL PART.



“Uracilcarbonsäureäthylester” was prepared according to his directions.² It was found that 18 grams of oxalacetic ethyl ester, after 2 weeks, gave a little over 4 grams of uracil-4-ethylcarboxylate and that 60 grams of oxalacetic ethyl ester gave about 12 grams of the crude pyrimidine.

The ester was saponified as follows: Five grams were dissolved in about 60 cc. of hot alcohol and twice the calculated amount of potassium hydroxide (3 grams) in 10 cc. of water, was added; the whole then solidified to a thick mass. A clear solution was obtained by adding about 150 cc. of water. This was then evaporated to a small volume and the acid was precipitated by adding dilute hydrochloric acid in excess. The yield was near the calculated. The acid is very difficultly soluble in alcohol. It was purified for analysis by crystallizing from water. It is moderately soluble in hot water, difficultly soluble in cold, and it separates in the form of microscopic, stout, twinned prisms, some in the form of a cross.

0.6929 gram substance lost 0.0712 gram of water when heated 1 hour at 125°–130°.

	Calculated for $C_5H_4O_4N_2 \cdot H_2O$.	Found.
H_2O	10.34	10.26
N	16.09	16.12

¹ J. Chem. Soc. Proc., **16**, 121 (1900).

² J. prakt. Chem., **56**, 488 (1897).

The acid usually melts at 347° with strong effervescence; occasionally samples were obtained which decomposed on heating without effervescence. It gives a white, amorphous precipitate with silver nitrate, soluble in nitric acid. The aqueous solution gives a crystalline precipitate with barium chloride. When heated (0.5 gram) with 20 per cent sulphuric acid (5 cc.) at 185° – 208° , for 2 hours, no uracil was formed. A portion of the solution was tested with bromine water and barium hydroxide¹ for uracil, but no color whatever was obtained. Therefore, there could not have been as much as 0.005 gram of uracil formed. The material remaining was crystallized from water, whereupon it melted at 347° with vigorous effervescence.

It was found that the acid (0.5 gram) was not attacked by fuming nitric acid (10 cc.) when boiled and then evaporated to dryness on the water-bath. The operation was repeated with 20 cc. of fuming nitric acid. There sidue then, when crystallized from water, melted with effervescence at 347° . This experiment shows that in the preparation of nitrouracilcarboxylic acid,² by nitrating 4-methyluracil, it is the 5-position that is first attacked.

Action of Bromine Water: Dibrombarbituric Acid.—Three grams of the above acid were suspended in 20 cc. of water and 6 grams of bromine added. Carbon dioxide was given off, and the acid slowly dissolved when more bromine was added. The solution was evaporated in a flat dish at about 50° . It then deposited long, colorless, flat, narrow prisms; one that separated was 2.5 inches in length.

	Calculated for $C_4H_2O_8N_2Br_2$.	I.	Found. II.	III.
N	9.79	10.04	9.87	. .
Br	55.94	.	.	56.49

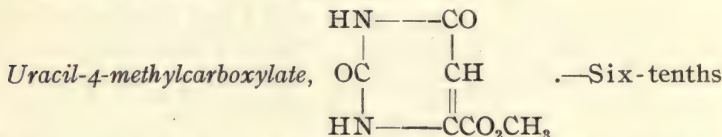
This material was compared with some dibrombarbituric acid, prepared by treating barbituric acid with bromine and water, as above. Similar crystals were obtained. Both preparations had the following properties: they melted,

¹ J. Biol. Chem., **3**, 1907.

² Behrend: Ann. Chem. (Liebig), **229**, 36 (1885).

when heated under the same conditions, with effervescence, at 235° , and the melting or decomposing point was not altered when the two were mixed. Ammonium or barium hydroxide gave no color.

When hydrogen sulphide was passed into the aqueous solution sulphur separated, and then, on boiling off the excess of hydrogen sulphide and adding barium hydroxide, a purple or violet-blue precipitate was formed. Baeyer¹ has shown that dibrombarbituric acid gives dialuric acid when treated with hydrogen sulphide, and dialuric acid gives a violet-blue precipitate with barium hydroxide, as observed by Behrend and Roosen.² The samples in alcohol gave precipitates having the same appearance when mixed with alcoholic solutions of thiourea and ammonium thiocyanate.



of a gram of uracil-4-carboxylic acid was suspended in 100 cc. of methyl alcohol and saturated with hydrogen chloride. After warming a day the acid dissolved, and on cooling a mass of colorless needles separated. This ester formed needles or prisms from water and it melted to an oil at 230° .

	Calculated for $\text{C}_5\text{H}_6\text{O}_4\text{N}_2$	Found.
N	16.47	16.45

The Potassium Salt, $\text{C}_5\text{H}_3\text{O}_4\text{N}_2\text{K}$.—This normal salt was formed when the acid and potassium hydroxide, in molecular proportions, were mixed in aqueous solution. Uracil-5-carboxylic acid, under these conditions, gives an acid salt. It separated on cooling the aqueous solution as a felt-like mass of fine, colorless needles. It showed no signs of melting at 355° .

	Calculated for $\text{C}_5\text{H}_3\text{O}_4\text{N}_2\text{K}$.	I.	Found.	II.
N	14.43	14.23		14.17

¹ Ann. Chem. (Liebig), **130**, 133 (1864)

² *Ibid.*, **251**, 244 (1889).

The Barium Salt, $(C_5H_3O_4N_2)_2Ba$.—This salt separates in the form of needles or prisms when hot aqueous solutions of the acid and barium chloride are mixed.

	Calculated for $C_{10}H_6O_8N_4Ba$.	I.	Found.	II.
N	12.51	12.12		12.20

Oxalaceticethyl Ester and Ethylpseudothiourea Hydrobromide.—Fifty grams of Kahlbaum's oxalaceticethyl ester, 50 grams of the ethyl bromide addition product of thiourea, and 22 grams of sodium hydroxide, in a little over 100 cc. of cold water, were mixed and allowed to stand over night. The next day about 10 grams of crystalline material had separated. This was found to be difficultly soluble in water and readily soluble in hot alcohol. When crystallized from a mixture of equal volumes of alcohol and water it formed balls of colorless needles, which melted to a clear oil at 133° – 134° . The analytical results and the behavior of the substance agreed with the view that this substance is an addition product.

	Calculated for $C_{11}H_{20}O_6N_2S$.	I.	Found.	III.
N	9.58	9.33	9.43	9.32

When this substance was boiled with hydrochloric or hydrobromic acid it gave a product which melted at 206° – 207° . This was very soluble in alcohol. From water it separated in the form of needles or prisms. It contained sulphur, but no nitrogen, and since it was not a pyrimidine it was not further examined. The alkaline solution from which the addition product had separated was acidified with hydrochloric acid; a small amount of oil separated but no mercaptopyrimidine.

Acetylethylcyanacetate and Ethylpseudothiourea Hydrobromide.—Fifteen grams of acetylethylcyanacetate, prepared by Haller's method,¹ were mixed with 18 grams of the ethyl bromide addition product of thiourea in 18 cc. of water and then 12 grams of potassium hydroxide in a little cold water added. This produced a white precipitate, which, after stand-

¹ Ann. Chim. Phys. [6], 17, 207 (1889).

ing over night, weighed 8.4 grams. When this was crystallized from alcohol it gave colorless, twinned, flat prisms, having the form of the letters x and y . They melted at 159° , with effervescence, and were found to be free from ash. The analytical results agreed with the calculated for an addition product of equal molecules of the pseudourea and acetylethylcyanacetate. Acids produced no precipitate in the alkaline filtrate from this material.

	Calculated for $C_{10}H_{17}O_3N_3S$.	I.	Found. II.
N	16.21	16.23	15.86

When boiled with alkali, acids or acetic anhydride, the substance decomposed.

Oxalmalonic Ethyl Ester¹ and Ethylpseudothiourea Hydrobromide.—These substances were mixed with potassium hydroxide in molecular proportions in aqueous solution. On standing over night, crystals separated; they were very soluble in hot water and somewhat less so in alcohol, from which solvent the material crystallized in the form of shining scales, which melted, with effervescence, at 181° . This material gave analytical results agreeing with the calculated for an addition product of 2 molecules of the pseudourea to 1 molecule of oxalmalonic ethyl ester.

	Calculated for $C_{17}H_{32}O_7N_4S_2$.	I.	Found. II.
N	11.96	11.95	12.08

When two molecular proportions of potassium hydroxide were used, a granular potassium salt separated which was free from sulphur.

NEW HAVEN, CONN.,
May, 1907.

¹ Bouveault: Bull. Soc. Chim. [3], 19, 78 (1898).

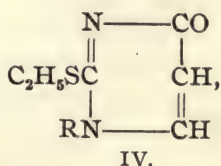
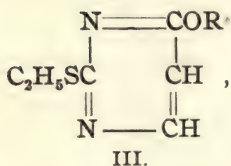
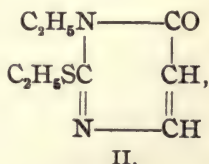
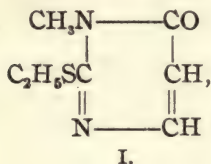
Contributions from the Sheffield Laboratory of Yale University.

CXLV.—RESEARCHES ON PYRIMIDINES: THE ACTION OF METHYL IODIDE ON 2-ANILINO-6-OXYPYRIMIDINE, AND THE SYNTHESIS OF 2-ANILINOPYRIMIDINE.

[TWENTY-FIRST PAPER.]

BY TRENT B. JOHNSON AND F. W. HEYL.

The writers have shown, in a previous paper,¹ that methyl iodide and ethyl iodide react with 2-ethylmercapto-6-oxypyrimidine in presence of alkali, giving 1-methyl-2-ethylmercapto-6-oxypyrimidine, I., and 1-ethyl-2-ethylmercapto-6-oxypyrimidine, II. The formation of isomeric oxygen derivatives, III., or 3-alkyl pyrimidines, IV., was not observed.

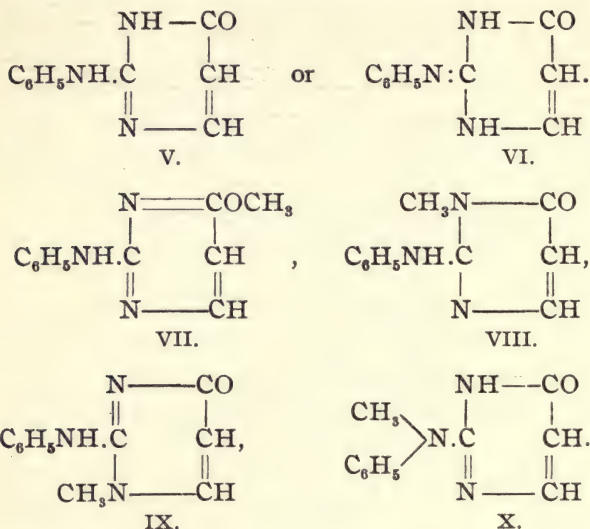


It seemed of interest to examine the behavior of methyl iodide towards 2-anilino-6-oxypyrimidine,² V. This pyr-

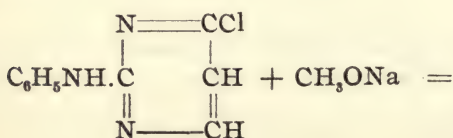
¹ THIS JOURNAL, 37, 628.

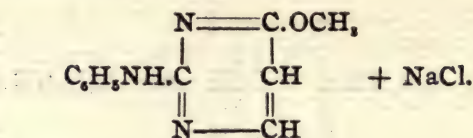
² J. Biol. Chem., 1, 305 (1906).

imidine, theoretically, might give 4 isomeric monomethyl derivatives, *viz.*, 2-anilino-6-methoxypyrimidine, VII., 1-methyl-2-anilino-6-oxypyrimidine, VIII., 2-anilino-3-methyl-6-oxypyrimidine, IX., and 2-methylanilino-6-oxypyrimidine, X.

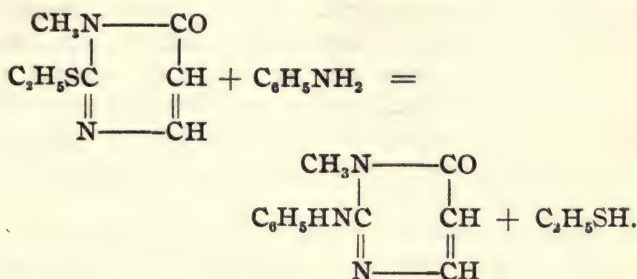


We find that 2-anilino-6-oxypyrimidine, V., reacts with methyl iodide, in the presence of potassium hydroxide, giving two monomethyl derivatives—2-anilino-6-methoxypyrimidine, VII., and 1-methyl-2-anilino-6-oxypyrimidine, VIII. The structure of these two pyrimidines was shown in the following manner: The same methoxypyrimidine (m. p. 119°) was obtained when 2-anilino-6-chloropyrimidine was warmed with sodium methylate. A quantitative yield of the pyrimidine was also formed when methyl iodide was allowed to act on the silver salt of 2-anilino-6-oxypyrimidine at ordinary temperature.

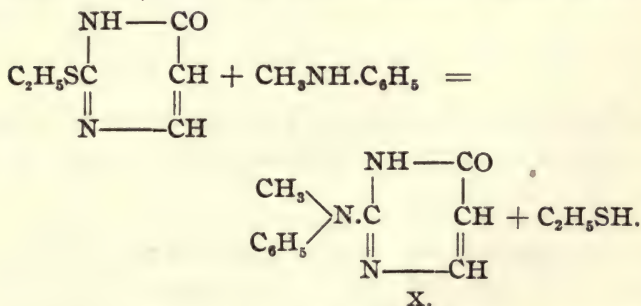




The second isomer was identical with the methyl pyrimidine obtained by heating 1-methyl-2-ethylmercapto-6-oxypyrimidine,¹ I., with aniline at 150°. It was soluble in alkali and

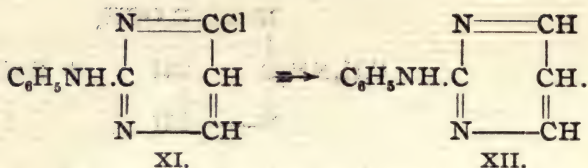


melted at 149°-150°. The isomeric 2-methylanilino-6-oxypyrimidine, X., which was prepared by heating 2-ethylmercapto-6-oxypyrimidine with methyl aniline, melted at 187°.



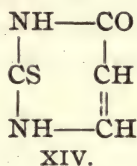
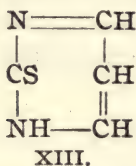
2-Anilino-6-oxypyrimidine reacts in a smooth manner with phosphorus oxychloride to give 2-anilino-6-chlorpyrimidine, XI. When this was digested with water and zinc dust it was reduced practically quantitatively to 2-anilinopyrimidine, XII.

¹ Johnson and Heyl: *Loc. cit.*



All attempts to hydrolyze 2-anilinopyrimidine, XII., and 2-anilino-6-oxypyrimidine to 2-oxypyrimidine and uracil, respectively, were unsuccessful. They could be digested for hours with concentrated hydrochloric acid without alteration. 2-Anilinopyrimidine was completely decomposed when heated with hydrochloric acid at 168°. On the other hand, 2-anilino-6-oxypyrimidine was not changed by this treatment, and was also recovered unaltered after heating with 20 per cent sulphuric acid at 230°.

The above pyrimidines might be expected to react with carbon bisulphide, giving 2-thiopyrimidine, XIII., and 2-thio-uracil, XIV., with formation of phenylisocyanate. We find,



on the other hand, that they are extremely stable in presence of this reagent, and were recovered unaltered after heating with carbon bisulphide at 230°.

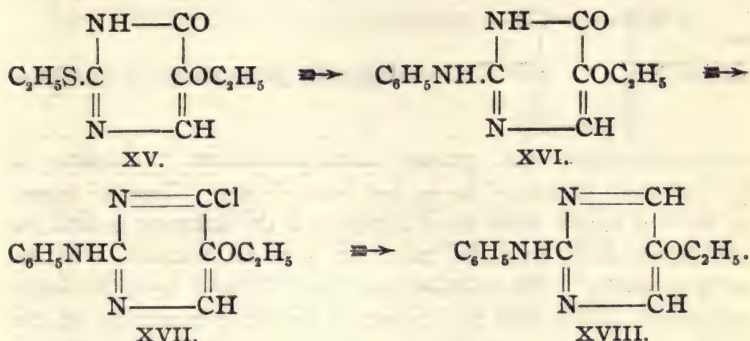
We examined, in the course of our work, the action of aniline and ammonia on 2-ethylmercapto-5-ethoxy-6-oxypyrimidine,¹ XV. We find that this mercaptopyrimidine shows no tendency to react with aniline at 100°. In order to introduce the anilino group it was necessary to heat for several hours at 200°. This behavior is of interest since 2-ethylmercapto-6-oxypyrimidine² and 2-ethylmercapto-5-brom-6-oxypyrimidine³ react with aniline at 100° to give quantitative

¹ Johnson and McCollum: *J. Biol. Chem.*, **1**, 437.

² Johnson and Johns: *Loc. cit.*

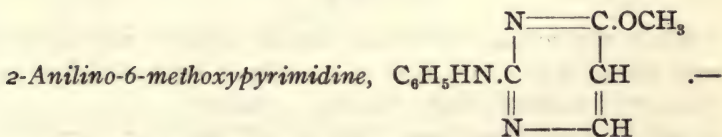
³ Wheeler and Bristol: *THIS JOURNAL*, **33**, 437.

yields of the corresponding 2-anilinopyrimidines. 2-Ethylmercapto-5-ethoxy-6-oxypyrimidine was also recovered unaltered after heating with ammonia at 230°.



2-Anilino-5-ethoxy-6-oxypyrimidine, XVI., reacted with phosphorus oxychloride to give a good yield of 2-anilino-5-ethoxy-6-chlorpyrimidine, XVII. When this chloride was heated with ammonia a quantitative yield of 2-anilino-5-ethoxy-6-aminopyrimidine was obtained. 2-Anilino-5-ethoxy-pyrimidine, XVIII., was prepared by reducing the chlorpyrimidine, XVII., with zinc dust.

EXPERIMENTAL.

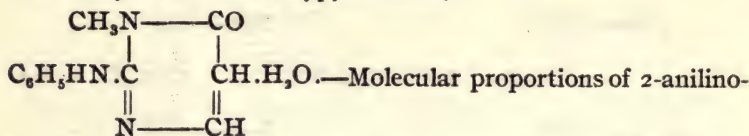


This pyrimidine was obtained when methyl iodide was allowed to act on the silver salt of 2-anilino-6-oxypyrimidine¹ at ordinary temperature. It was also prepared by treating 2-anilino-6-chlorpyrimidine with sodium methylate. It deposited from 95 per cent alcohol in transparent prisms that melted at 119° to a clear oil. It was converted into 2-anilino-6-oxypyrimidine (m. p. 231°) when digested with 20 per cent hydrochloric acid. Analysis (Kjeldahl):

¹ Johnson and Johns: *Loc. cit.*

	Calculated for $C_{11}H_{11}ON_3$.	Found.
N	20.89	20.93

1-Methyl-2-anilino-6-oxypyrimidine,



6-oxypyrimidine (20 grams) and potassium hydroxide (6 grams) were dissolved in 95 per cent alcohol. Twenty grams of methyl iodide were then added and the solution heated on the steam-bath until it failed to give an alkaline reaction with turmeric. The solution was then filtered from insoluble potassium iodide and the excess of alcohol evaporated on the steam-bath. We obtained a syrup which deposited a crystalline precipitate when treated with cold water. This was separated and triturated with a 10 per cent sodium hydroxide solution and the insoluble portion purified by crystallization from 95 per cent alcohol. It separated in prismatic crystals that melted at 119° to a clear oil. It was identified as *2-anilino-6-methoxypyrimidine*. A mixture of the 2 compounds melted sharp at 119° . Analysis (Kjeldahl):

	Calculated for $C_{11}H_{11}ON_3$.	Found.
N	20.89	21.2

When the sodium hydroxide filtrate (above) was acidified with acetic acid a mixture of 2-anilino-6-oxypyrimidine and 1-methyl-2-anilino-6-oxypyrimidine separated. After a fractional crystallization from alcohol and repeated recrystallizations from benzene and water the methylpyrimidine was obtained pure. It deposited from hot water in slender prisms, that melted at 149° – 150° to a clear oil. It contained 1 molecule of water of crystallization, which was determined by heating at 100° – 110° .

0.8187 gram substance lost 0.0686 gram.

	Calculated for $C_{11}H_{11}ON_3.H_2O$.	Found.
H ₂ O	8.21	8.37

Analysis of anhydrous material:

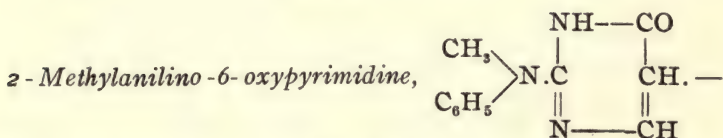
0.2333 gram substance gave 0.5597 gram CO_2 and 0.1130 gram H_2O .

Nitrogen determined by Kjeldahl method:

	Calculated for $\text{C}_{11}\text{H}_{11}\text{ON}_3$.	Found.
C	65.43	65.67
H	5.38	5.47
N	20.89	20.55

*Action of Aniline on 1-Methyl-2-ethylmercapto-6-oxypyrimidine.*¹—The mercaptopyrimidine was recovered unaltered after heating with aniline for several hours at 100° . One and two-tenths grams of the mercaptopyrimidine and 0.7 gram of aniline were heated for 7 hours at 125° – 155° . The excess of aniline was then removed by distillation with steam and the insoluble residue treated with hot benzene. A crystalline compound separated from the benzene on cooling. It was purified by recrystallization from water and deposited in prisms that melted at 149° – 150° . When this derivative was mixed with some 1-methyl-2-anilino-6-oxypyrimidine (m. p. 149° – 150°), the melting point was not changed. Analysis (Kjeldahl):

	Calculated for $\text{C}_{11}\text{H}_{11}\text{ON}_3$.	Found.
N	20.89	20.6

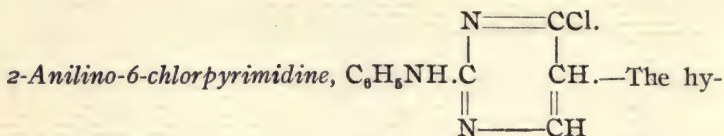


This pyrimidine was prepared by heating 7 grams of 2-ethylmercapto-6-oxypyrimidine² with 6 grams of methyl aniline for 14 hours at 100° . It was soluble in warm benzene and alcohol. It separated from hot alcohol in large, prismatic crystals that melted at 187° to a clear oil. The yield corresponded to about 74 per cent of the theoretical. Analysis (Kjeldahl):

¹ Johnson and Heyl: *Loc. cit.*

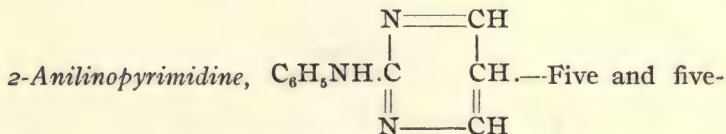
² Wheeler and Merriam: *THIS JOURNAL*, **29**, 478 (1903).

	Calculated for $C_{11}H_{11}ON_3$.	I.	Found. II.
N	20.89	20.55	20.66



drochloride of this pyrimidine was obtained when 2-anilino-6-oxypyrimidine was warmed with an excess of phosphorus oxychloride. After the evolution of hydrochloric acid had ceased the solution was poured upon crushed ice to destroy the excess of phosphorus oxychloride. The hydrochloride of 2-anilino-6-chlorpyrimidine separated as a thick varnish, which soon solidified. This salt was triturated with a dilute solution of sodium hydroxide or ammonia when the chlorpyrimidine deposited. It crystallized from alcohol in plates that melted at 134° to an oil. Analysis (Kjeldahl):

	Calculated for $C_{10}H_8N_3Cl$.	I.	Found. II.
N	20.43	20.09	20.3



tenths grams of 2-anilino-6-chlorpyrimidine and 30 grams of zinc dust were suspended in 400 cc. of water and the mixture boiled for 2.5 hours. The solution was then filtered and the residue of zinc dust extracted twice with 300 cc. of boiling water. The aqueous filtrates were combined and concentrated to one-half their volume, when the anilinopyrimidine separated, on cooling, in characteristic, slender prisms. The yield was 3.3 grams, or 78 per cent of the theoretical. The base was practically insoluble in cold and difficultly soluble in hot water. It crystallized from 95 per cent alcohol in prismatic crystals that melted at 116° to a clear oil. Analysis (Kjeldahl):

	Calculated for $C_{10}H_9N_3$.	Found.
N	24.56	24.22

2-Anilinopyrimidine could be boiled with concentrated hydrochloric acid without change. One gram of the base was heated with about 5 cc. of concentrated hydrochloric acid for 2 hours at 148° – 168° . Under these conditions it was decomposed into tarry products, from which nothing definite was isolated. An attempt was made to convert 1-anilinopyrimidine into 2-thiopyrimidine by heating with carbon bisulphide. One gram of the pyrimidine was heated with 6 cc. of carbon bisulphide, for 4 hours at 190° – 195° . We obtained a clear solution which deposited beautiful, needle-like prisms that melted at 116° . The compound gave no test for sulphur and was identified as unaltered material.

The Hydrochloric Acid Salt.—This salt was extremely soluble in water and alcohol. It had no definite melting point, but decomposed when heated above 125° . Analysis (Kjeldahl):

	Calculated for $C_{10}H_9N_3.HCl$.	Found.
N	20.24	19.77

The Sulphuric Acid Salt.—This salt separated from 20 per cent sulphuric acid in elongated prisms that melted at 140° – 142° . The salt dissociates when warmed in aqueous solutions. Analysis:

	Calculated for $C_{10}H_9N_3.H_2SO_4$.	Calculated for $(C_{10}H_9N_3)_2H_2SO_4$.	Found.
N	15.5	19.09	15.10

The Platinum Chloride Double Salt.—This salt separated in yellow rosettes when a hydrochloric acid solution of the base was treated with hydrogen-platinic chloride. The salt was slowly decomposed in boiling water and metallic platinum deposited. It melted with decomposition at 218° – 221° .

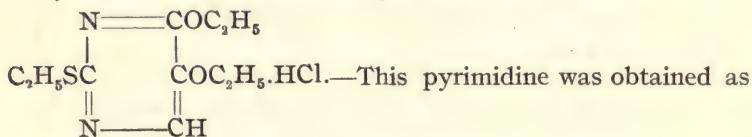
	Calculated for $(C_{10}H_9N_3.HCl)_2.PtCl_4$.	Found.
Pt	25.91	26.6

Behavior of 2-Anilino-6-oxypyrimidine towards Hydrochloric and Sulphuric Acids.—This pyrimidine is more stable in presence of acids than 2-anilinopyrimidine. It was recovered unaltered after heating with concentrated hydrochloric acid for 4 hours at 150° – 160° . It was not decomposed after heating with 25 per cent sulphuric acid at 230° for 2 hours.

Behavior of 2-Anilino-6-oxypyrimidine towards Carbon Bisulphide.—There were no indications of any reaction after heating 2 grams of the pyrimidine with 5 cc. of carbon bisulphide for 5 hours, at 150° – 160° . The mixture was then heated for 3 hours at 185° – 215° . When the tube was opened there was no pressure and the unaltered pyrimidine was recovered melting at 229° . In a third experiment 1 gram of the pyrimidine was heated with 5 cc. of carbon bisulphide for 6 hours, at 230° . When the tube was opened there was some pressure due to the presence of hydrogen sulphide and a crystalline residue was suspended in the carbon bisulphide. This was identified as the unaltered pyrimidine; it melted at 228° – 229° , and when mixed with 2-anilino-6-oxypyrimidine the melting point was not changed. Analysis (Kjeldahl):

	Calculated for $C_{10}H_9ON_3$.	Found.
N	22.46	22.17

Hydrochloride of 2-Ethylmercapto-5,6-diethoxypyrimidine,



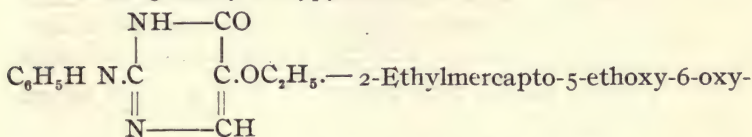
an oil by treatment of 2-ethylmercapto-5-ethoxy-6-chloropyrimidine¹ with the calculated quantity of sodium ethylate. When an ether solution of the pyrimidine was saturated with dry hydrochloric acid gas the salt deposited in prismatic crystals that melted with decomposition at 129° – 131° . The salt was hygroscopic. Analysis (Kjeldahl):

	Calculated for $C_{10}H_{13}O_2N_2S \cdot \text{HCl}$.	Found.
N	10.58	10.55

¹ Johnson and McCollum: J. Biol. Chem., 1, 443 (1906).

Action of Ammonia on 2-Methylmercapto-5-ethoxy-6-oxypyrimidine.—This mercapto pyrimidine was recovered unaltered after heating with concentrated alcoholic ammonia for 2 hours at 140°–160° and again for 1.5 hours at 210°–235°.

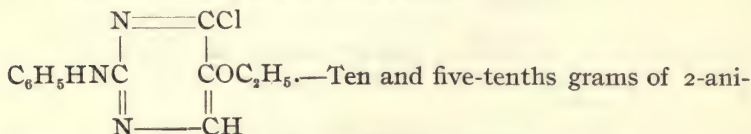
2-Anilino-5-ethoxy-6-oxypyrimidine,



pyrimidine¹ was recovered unaltered after heating with aniline on the steam-bath for several hours. Four grams of the mercaptopyrimidine and 2 grams of aniline were dissolved in 10 cc. of alcohol and heated for 2 hours at 185°–216°. When the tube was examined the presence of ethyl mercaptan was apparent, and a crystalline residue had deposited. This was a mixture of unaltered mercaptopyrimidine and the anilino derivative that melted above 160°. The anilino compound was separated from the mercapto derivative by dissolving in cold dilute hydrochloric acid and making alkaline with ammonia. The anilino derivative deposited in plates and was purified for analysis by recrystallization from alcohol. It melted at 231°–232°. In a second experiment we heated 10 grams of the mercaptopyrimidine and 5.1 grams of aniline for 6 hours at 190°–200° and obtained 6.8 grams of crude anilino compound melting at 214°–220°. We did not observe the formation of any 2,5-dianilino-6-oxypyrimidine under the conditions employed. Analysis (Kjeldahl):

	Calculated for $\text{C}_{12}\text{H}_{13}\text{O}_2\text{N}_3$.	Found.
N	18.18	18.10

2-Anilino-5-ethoxy-6-chlorpyrimidine,

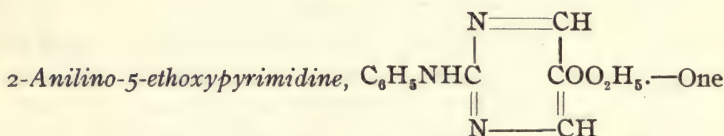


lino-5-ethoxy-6-oxypyrimidine were warmed with 30 cc. of

¹ Johnson and McCollum: *Loc. cit.*

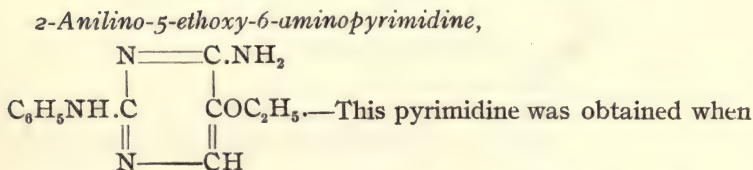
phosphorus oxychloride until the evolution of hydrochloric acid ceased. The solution was then poured upon crushed ice, when the chlorpyrimidine separated as a semi-solid. The chloride was dissolved in ether and thoroughly dried with calcium chloride. When the ether was evaporated the chloride deposited in prismatic crystals that were extremely soluble in organic solvents. The compound crystallized from alcohol in stout prisms, that melted at 111° – 112° to an oil. Analysis (Kjeldahl):

	Calculated for $C_{12}H_{12}ON_3Cl$.	Found.
N	16.82	16.55



gram of 2-anilino-5-ethoxy-6-chlorpyrimidine was digested for 1 hour with 10 grams of zinc dust and 150 cc. of water. When the hot mixture was filtered the pyrimidine deposited in prismatic crystals. It was difficultly soluble in water and more was obtained by repeatedly extracting the zinc residue with hot water. The pyrimidine dissolves in concentrated sulphuric acid to give a yellow solution. It crystallized from 95 per cent alcohol in short prisms that melted to a clear oil at 130° – 131° . Analysis (Kjeldahl):

	Calculated for $C_{12}H_{13}ON_3$.	I.	Found.	II.
N	19.53	18.98		19.33



2-anilino-5-ethoxy-6-chlorpyrimidine was heated with alcoholic ammonia at 180° – 188° . When 1 gram of the chloride was heated with alcoholic ammonia, for 2 hours, at 150° ,

the reaction was not complete, and the product obtained gave a pronounced test for chlorine after crystallization from alcohol. The pyrimidine crystallized from 95 per cent alcohol in prisms that melted at 133° – 134° to a clear oil. Analysis (Kjeldahl):

	Calculated for $C_{12}H_{14}ON_4$	Found.
N	24.34	24.06

NEW HAVEN, CONN.,
June 15. 1907.

The reaction was not completed and the product was a pronounced test for chlorine. The product was not. The pyridine crystallized from the mother liquor in prisms that melted at 133° - 134° to a clear oil. (Kjeldahl):

Found.	Calculated for $C_{10}H_{10}N_2$	N	New Haven, Conn., June 12, 1907.
24.66	24.74		

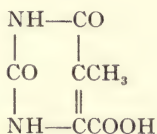
VI.—RESEARCHES ON PYRIMIDINS: SYNTHESIS OF THYMIN-4-CARBOXYLIC ACID.

By TREAT B. JOHNSON.

(From the Sheffield Laboratory of Yale University.)

(Received for publication, June 27, 1907.)

I shall describe, in this paper, the preparation and properties of thymin-4-carboxylic acid,



The study of the carboxylic acids of uracil, cytosin and thymin is of interest on account of the possibility that these pyrimidins may be linked in nucleic acids by acid amide groupings, —CO.NH. It has already been shown¹ that uracil may exist in nucleic acids as a 5-carboxyl compound since uracil-5-carboxylic acid can be quantitatively converted into uracil if heated with 20 per cent sulphuric acid at 160–170°. I now find that thymin-4-carboxylic acid can be heated with 20 per cent sulphuric acid, under the same conditions, without alteration. *Thymin therefore cannot exist in the nucleic acids as a 4-carboxyl compound.*

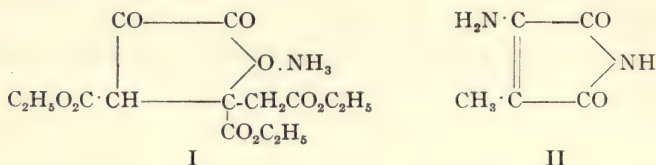
Wislicenus observed that diethyl oxalacetate and its homologues show a wide difference in their behavior towards ammonia and amines. Diethyl oxalacetate, for example, combines with ammonia to form an unstable addition product, which is changed to an ammonium salt of the lactone ester of oxalcitric acid (I)² when warmed with alcohol.

Diethyl methyloxalacetate, on the other hand, does not form

¹ *Amer. Chem. Journ.*, xxxvii, p. 392.

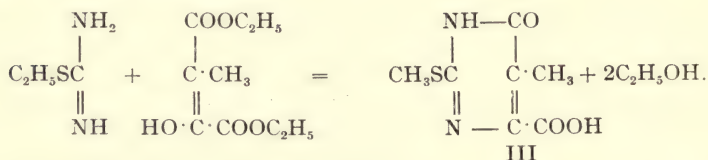
² Wislicenus and Beckh: *Ber. d. deutsch. chem. Gesellsch.*, xxviii, p. 789; *Ann. d. Chem.* (Liebig), ccxcv, p. 339.

an addition product with ammonia but reacts at 110° , giving aminomethylmaleinimide (II).¹



Another striking example of this difference between diethyl oxalacetate and diethyl methyloxalacetate was found when we investigated the behavior of pseudothioureas towards these esters. Pseudoethylthiourea combines with diethyl oxalacetate, giving a stable addition product (Professor Wheeler).

On the other hand, diethyl methyloxalacetate reacts with pseudomethylthiourea, in presence of potassium hydroxide, giving a good yield of the potassium salt of 2-methylmercapto-4-carboxyl-5-methyl-6-oxypyrimidin (III). The condensation can be represented as follows:



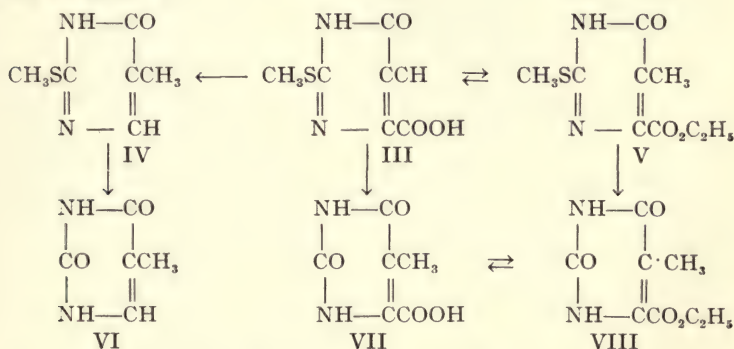
2-Methylmercapto-4-carbethoxy-5-methyl-6-oxypyrimidin (V) was obtained, in one experiment, as a secondary product of the condensation.

2-Methylmercapto-4-carboxyl-5-methyl-6-oxypyrimidin (III) can be converted into thymine-4-carboxylic acid (VII), by digesting with concentrated hydrochloric acid. When this acid was boiled, in ethyl alcohol solution, with a small quantity of sulphuric acid it was converted into thymine-4-ethylcarboxylate (VIII). This same ester was also obtained when 2-methylmercapto-4-carbethoxy-5-methyl-6-oxypyrimidin (V), was boiled in alcoholic solution with sulphuric acid. When thymine-4-carboxylic acid (VII), is melted it undergoes complete decom-

¹ Wislicenus and Kiesewetter: *Ber. d. deutsch. chem. Gesellsch.*, xxxi, p. 194.

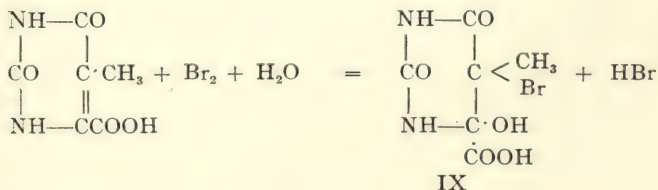
position. On the other hand, 2-methylmercapto-4-carboxyl-5-methyl-6-oxypyrimidin (III), melts with evolution of carbon-dioxide and is converted quantitatively into 2-methylmercapto-5-methyl-6-oxypyrimidin (IV). This mercaptopyrimidin can then be changed to thymin (VI) by boiling with hydrochloric acid.¹

The formation of thymin in this manner from 2-methylmercapto-4-carboxyl-5-methyl-6-oxypyrimidin (III), shows that the condensation takes place as represented in the preceding equation and that the product is not a hydantoin derivative. The above compounds and their various transformations are represented as follows:



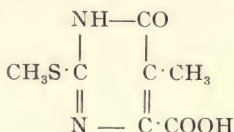
Thymin-4-carboxylic acid is characterized by its insolubility in cold water and by its property of crystallizing from aqueous solution with and without water of crystallization. It gives very insoluble barium and lead salts, and is not precipitated by phosphotungstic acid.

Thymin-4-carboxylic acid reacts in the normal manner with bromine water giving oxybromthymin-4-carboxylic acid (IX).



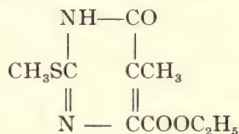
¹ *Amer. Chem. Journ.*, xxix, p. 487.

EXPERIMENTAL.

2-Methylmercapto-4-carboxyl-5-methyl-6-oxypyrimidin,

Thirty grams of pseudomethylthiourea hydriodide and 50 grams of the sodium salt of diethyl oxalpropionate were dissolved in about 500 cc. of water and two molecular proportions of potassium hydroxide (16 grams) added to the solution. The mixture was allowed to stand on the steam-oven for 8–10 hours and then concentrated to a volume of 150 cc. After thorough cooling, and acidifying with hydrochloric acid, the mercapto-pyrimidin deposited in prismatic crystals. It was practically insoluble in cold water and difficultly soluble in boiling water and alcohol. It separated from water or alcohol in rectangular prisms that melted at 243–244° with effervescence to a clear oil. It deposited from glacial acetic acid in stout prismatic crystals. The yield of acid corresponded to about 80 per cent of the theoretical. Analysis (Kjeldahl):

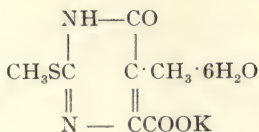
	Calculated for $\text{C}_7\text{H}_8\text{O}_3\text{N}_2\text{S}$:	Found:
N.....	14.00 per cent.	13.88 per cent.

2-Methylmercapto-4-carbethoxy-5-methyl-6-oxypyrimidin,

This ester was obtained, associated with 2-methylmercapto-4-carboxyl-5-methyl-6-oxypyrimidin, when I used one instead of two molecular proportions of potassium hydroxide in the above condensation. It was difficultly soluble in cold water and alcohol, but deposited from hot alcohol or water in slender needles that melted at 201–202° to a clear oil without effervescence. Analysis (Kjeldahl):

	Calculated for $\text{C}_9\text{H}_{12}\text{O}_3\text{N}_2\text{S}$:	Found:
N.....	12.30 per cent.	12.37 per cent.

Potassium Salt of 2-Methylmercapto-4-carboxyl-5-methyl-6-oxypyrimidin,



A good yield of this salt was obtained under the following conditions: Pseudomethylthiourea and diethyl oxalpropionate were condensed as in the above experiment, in presence of two molecular proportions of potassium hydroxide. After standing for about twelve hours at 40–45° the solution was then acidified with acetic acid and concentrated to a volume of about 150 cc. On cooling the potassium salt deposited in distorted needles that decomposed with effervescence when heated above 230°. When this acetic acid filtrate was treated with hydrochloric acid the mercapto-acid separated melting at 243°. The potassium salt was very soluble in hot water and deposited, on cooling, in needles. They contained water of crystallization which was determined by heating at 100–110° for two hours.

1. 2424 gram substance lost 0.4032 gram water.

	Calculated for $\text{C}_7\text{H}_7\text{O}_3\text{N}_2\text{SK} \cdot 6 \text{H}_2\text{O}$:	Found:
H_2O	31.21 per cent.	32.4 per cent.

Nitrogen determination in the anhydrous salt (Kjeldahl):

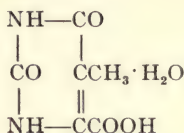
	Calculated for $\text{C}_7\text{H}_7\text{O}_3\text{N}_2\text{SK}$:	Found:
N.....	11.76 per cent.	11.91 per cent.

Behavior of 2-Methylmercapto-4-carboxyl-5-methyl-6-oxypyrimidin on Heating.—About two grams of the mercapto-acid were heated in a sulphuric acid bath at 245° until all effervescence ceased. I obtained a clear oil that crystallized, on cooling, in large, prismatic crystals. When these prisms were heated they melted sharply at 230–231° without effervescence to a clear oil. The compound deposited from water in flat prisms that melted at 233° and was identified as 2-methylmercapto-5-methyl-6-oxypyrimidin.

pyrimidin.¹ When mixed with this pyrimidin the melting point was not lowered. Analysis (Kjeldahl):

	Calculated for $C_6H_8ON_2S$:	Found:
N.....	17.94 per cent.	17.80 per cent.

Thymin-4-carboxylic Acid,



A quantitative yield of this acid was obtained when 2-methyl-mercapto-4-carboxyl-5-methyl-6-oxypyrimidin was digested with concentrated hydrochloric acid. The oxygen acid separated from the acid solution as a granular powder that was difficultly soluble in boiling water and practically insoluble in alcohol. A most characteristic behavior of this acid is its property of crystallizing from hot water in anhydrous condition and with one molecule of water of crystallization. When a hot, saturated aqueous solution of the acid was allowed to cool slowly the anhydrous acid first deposited in balls of microscopic prisms resembling very much the crystalline form of uracil. They decomposed at 328–330° (Anschutz thermometer) and did not lose weight when heated at 120°. Analysis (Kjeldahl):

	Calculated for $C_6H_8O_4N_2$:	Found:
N.....	16.47 per cent.	16.37 per cent.

After filtering from the anhydrous acid and allowing the filtrate to stand, transparent, rectangular prisms of the hydrous acid deposited. They decomposed at the same temperature as the anhydrous acid (328–330°). The acid was not precipitated by phosphotungstic acid.

Water determination: 0.6742 gram substance lost 0.0687 gram water after heating one hour at 110–120°.

	Calculated for $C_6H_8O_4N_2 \cdot H_2O$:	Found:
H_2O	9.60 per cent.	10.1 per cent.

¹ *Amer. Chem. Journ.*, xix, p. 478.

Analysis of the anhydrous acid: 0.2592 gram substance gave 0.4002 gram CO_2 and 0.0854 gram H_2O . Nitrogen determination (Kjeldahl):

	Calculated for $\text{C}_6\text{H}_5\text{O}_4\text{N}_2$:	Found:
C.....	42.35 per cent.	42.11 per cent.
H.....	3.52 " "	3.66 " "
N.....	16.47 " "	16.23 " "

Action of 20 per cent Sulphuric Acid.—One-half a gram of the thymine acid was heated with 5 cc. of 20 per cent sulphuric acid for two hours at 160 – 170° . When the tube was opened there was no pressure and the unaltered acid was suspended in the sulphuric acid. I recovered 0.45 gram of acid melting at 326 – 329° . Analysis (Kjeldahl):

	Calculated for $\text{C}_6\text{H}_5\text{O}_4\text{N}_2$:	Found:
N.....	16.47 per cent.	16.15 per cent.

Potassium Salt, $\text{C}_6\text{H}_5\text{O}_4\text{N}_2\text{K} \cdot 2\text{H}_2\text{O}$.—This salt was prepared by dissolving molecular proportions of potassium hydroxide and thymine-4-carboxylic acid in water. When the solution was concentrated and allowed to stand for a few hours the salt deposited in radiating prisms. It was dried for analysis in a desiccator over sulphuric acid (Kjeldahl):

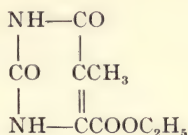
	Calculated for $\text{C}_6\text{H}_5\text{O}_4\text{N}_2\text{K}$:	Calculated for $\text{C}_6\text{H}_5\text{O}_4\text{N}_2\text{K} \cdot 2\text{H}_2\text{O}$:	Found:
N.....	13.45 per cent.	11.06 per cent.	10.97 per cent.

Lead Salt $(\text{C}_6\text{H}_5\text{O}_4\text{N}_2)_2\text{Pb}$.—This salt deposited in well developed prisms when a solution of lead acetate was added to a hot, saturated, aqueous solution of thymine-4-carboxylic acid. It was practically insoluble in cold water. Analysis (Kjeldahl):

	Calculated for $(\text{C}_6\text{H}_5\text{O}_4\text{N}_2)_2\text{Pb}$:	Found:
N.....	10.27 per cent.	10.00 per cent.

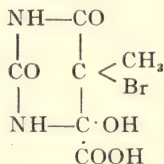
Barium Salt $(\text{C}_6\text{H}_5\text{O}_4\text{N}_2)_2\text{Ba}$.—Thymine-4-carboxylic acid gives no precipitate when treated with a solution of barium chloride. The barium salt was prepared by dissolving the acid in potassium hydroxide and then adding the calculated amount of barium chloride. It separated from water in corpuscular crystals. Analysis (Kjeldahl):

	Calculated for $(\text{C}_6\text{H}_5\text{O}_4\text{N}_2)_2\text{Ba}$:	Found:
N.....	11.77 per cent.	11.30 per cent.

Thymin-4-ethylcarboxylate,

was prepared by esterifying the acid with ethyl alcohol and sulphuric acid. It was also obtained when 2-methylmercapto-4-carbethoxy-5-methyl-6-oxypyrimidin was boiled in alcoholic solution with a small amount of hydrochloric acid. The ester deposited from hot water in distorted prisms that melted at 255° to a clear oil without effervescence. Analysis (Kjeldahl):

	Calculated for $\text{C}_8\text{H}_{10}\text{O}_4\text{N}_2$:	Found:
N.....	14.14 per cent.	14.07 per cent.

Oxybromhydrothymin-4-carboxylic Acid,

Three and five-tenths grams of finely pulverized thymin-4-carboxylic acid were suspended in about 40 cc. of bromine water and bromine slowly added until the acid had completely dissolved. There was no evolution of carbon dioxide and when the solution was allowed to evaporate spontaneously in the atmosphere well-developed, prismatic crystals of the hydro-derivative separated. It was purified for analysis by recrystallization from bromine water. It crystallized in small, prismatic crystals that charred when heated above 270° and then decomposed with violent effervescence from 295 – 300° according to the rate of heating. When thymin-4-carboxylic acid was heated with bromine water at 146 – 152° it was completely decomposed with formation of bromoform. Analysis (Kjeldahl):

	Calculated for $\text{C}_6\text{H}_7\text{O}_5\text{N}_2\text{Br}$:	Calculated for $\text{C}_5\text{H}_5\text{O}_3\text{N}_2\text{Br}$:	Found:	
			I.	II.
N.....	10.48 per cent.	12.66 per cent.	10.45	10.45 per cent.

[Reprinted from the American Chemical Journal, Vol. XXXVIII.
No. 5. November, 1907.]

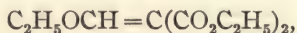
Contributions from the Sheffield Laboratory of Yale University.

CXLIX. — RESEARCHES ON PYRIMIDINES: SYN-
THESIS OF CYTOSINE-5-CARBOXYLIC ACID.

(TWENTY-SIXTH PAPER.)

BY HENRY L. WHEELER AND CARL O. JOHNS.

The present work was undertaken with the object of making a study of some material to be used for further syntheses, and also in order to examine the properties of cytosine-5-carboxylic acid and some of its derivatives. The acid has now been prepared by means of the following reactions: In a previous paper¹ we showed that ethoxymethylenmalonic ester,



in alkaline solution, condenses normally with ethylpseudothiourea, $\text{H}_2\text{N}-\text{C}(\text{SC}_2\text{H}_5)=\text{NH}$, giving 2-ethylmercapto-5-

¹ THIS JOURNAL, 37, 392 (1907).

carbethoxy-6-oxypyrimidine (I.). We now find that this cyclo amide reacts smoothly with phosphorus oxychloride, yielding an oil which is the imide chloride, 2-ethylmercapto-5-carbethoxy-6-chlorpyrimidine (II.). The transformation of this into 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine (III.), on standing with alcoholic ammonia at ordinary temperature, is also a perfectly smooth reaction. The imide chloride, therefore, in this case, is far more reactive than 2-ethylmercapto-6-chlorpyrimidine. The latter does not react on standing overnight with alcoholic ammonia, but it does react in a short time at 120°.

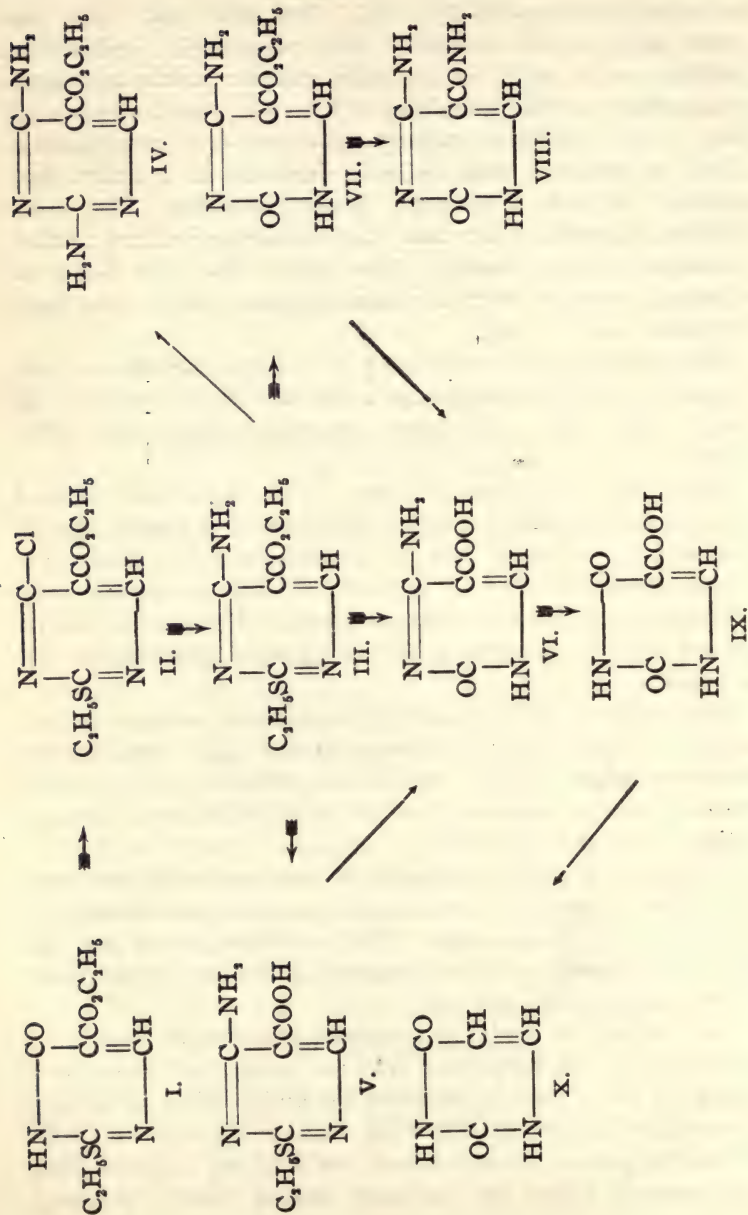
When the mercaptoamino ester (III.) is heated with alcoholic ammonia the mercapto group is the first to be removed (at about 170°) and 2,6-diamino-5-carbethoxypyrimidine (IV.) results.

When the mercaptoamino ester (III.) is carefully warmed with dilute alcoholic potassium hydroxide it is readily saponified and a potassium salt of 2-ethylmercapto-5-carboxyl-6-amino-pyrimidine (V.) is formed. If the treatment with potassium hydroxide is more energetic, mercaptan is also removed and the potassium salt of cytosine-5-carboxylic acid is obtained (VI.).

The moderate action of strong hydrochloric acid on 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine (III.) first removes ethylmercaptan, giving 5-carbethoxycytosine (VII.), which with aqueous ammonia at 150° is partially converted into cytosine-5-carboxamide (VIII.).

Longer boiling with hydrochloric acid saponifies the ester (III.), both mercaptan and alcohol separate, and cytosine-5-carboxylic acid (VI.) results. The synthesis of the acid and the transformations of the new pyrimidines can be illustrated by the formulas on page 596.

The action of acids on cytosine-5-carboxylic acid (VI.) developed the interesting fact that the presence of the carboxyl radical in the 5-position rendered the amino group apparently more easily subject to hydrolysis than in the case of unsubstituted cytosine. It was found also that the 6-amino group was removed before the carboxyl radical when cytosine-5-

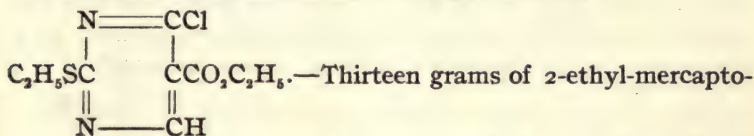


carboxylic acid was boiled with 20 per cent sulphuric acid, the chief product obtained being uracil-5-carboxylic acid (IX.), while only a small amount of cytosine was formed. Unless groups attached to cytosin-5-carboxylic acid would alter the course of hydrolysis, these results exclude the possibility that cytosin exists in the nucleic acids in the form of a 5-carboxyl derivative, or, in other words, it is not a grouping of this sort which is the source of cytosine.

Further action of acids, either at a high temperature, or on more prolonged boiling, strips all of the groups from the above compounds, leaving uracil (X.) as the last pyrimidine to be obtained.

EXPERIMENTAL PART.

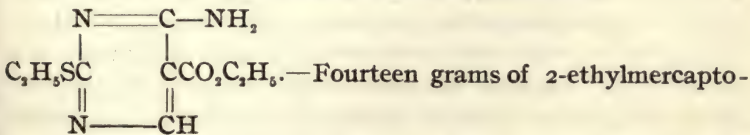
2-Ethylmercapto-5-carbethoxy-6-chlorpyrimidine,



5-carbethoxy-6-oxypyrimidine were boiled for two and a half hours with 40 cc. of phosphorus oxychloride. The phosphorus oxychloride was then removed by evaporation at 100° under diminished pressure. This left a syrup which was treated with cracked ice and the resulting oil, which did not solidify, was extracted with ether and dried over calcium chloride. It boiled at 203° at 20 mm. pressure. The yield of oil is almost quantitative and the crude product is pure enough to use for the following preparations without distilling. Nitrogen determinations in the case of the distilled product gave:

	Calculated for $\text{C}_9\text{H}_{11}\text{O}_2\text{N}_2\text{SCl}$.	I.	Found.	II.
N	11.35	11.33		11.31

2-Ethylmercapto-5-carbethoxy-6-aminopyrimidine,

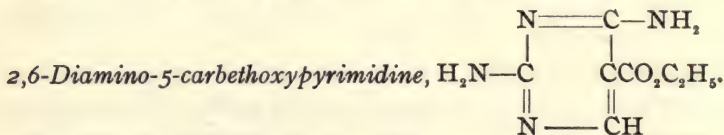


5-carbethoxy-6-chlorpyrimidine were added to a cold saturated

solution of alcoholic ammonia in a bottle. A reaction set in almost at once and a mass of crystals separated. The bottle was kept cool by means of ice-water. The material was allowed to stand overnight and then the alcohol and ammonia were evaporated and the residue treated with water. The yield was 90 per cent of the calculated. The resulting product melted to an oil in hot water but did not dissolve. It dissolved readily in hydrochloric acid. It was easily soluble in hot and moderately soluble in cold alcohol from which solvent it crystallized in rectangular plates melting at 102° . Analysis:

	Calculated for $C_9H_{13}O_2N_3S$.	I.	Found. II.
N	18.50	18.41	18.42

When this substance was boiled with strong hydrochloric acid for about one hour, the solution evaporated to dryness and the residue dissolved in sodium hydroxide and precipitated with acetic acid, cytosine-5-carboxylic acid was obtained.

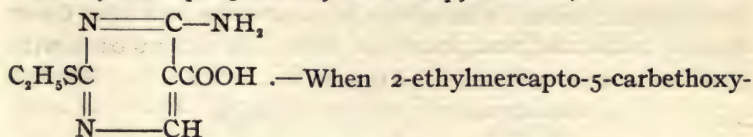


—This was obtained by heating the above 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine with a saturated solution of alcoholic ammonia at 168° – 178° for one and a half hours. When the tube became cool, a solid separated. The material was difficultly soluble in cold alcohol and water and it crystallized from alcohol in the form of needles melting to a clear oil at 205° – 207° . Analysis:

	Calculated for $C_7H_{10}O_2N_4$.	I.	Found. II.
N	30.76	30.62	30.76

This substance is soluble in hydrochloric acid from which solution it is reprecipitated by ammonia. The material which remained in the alcoholic mother-liquor from the above was found to be unaltered mercapto-derivative. Under the conditions of the experiment it appears that the carbethoxy group was not attacked.

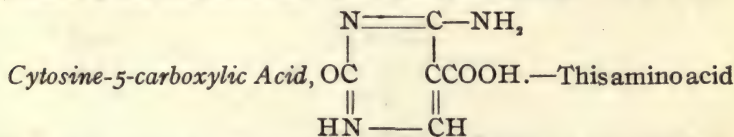
2-Ethylmercapto-5-carboxyl-6-aminopyrimidine,



6-aminopyrimidine in alcoholic solution was treated with an equal weight of potassium hydroxide in a small amount of water it was readily saponified. On evaporating to dryness the resulting residue dissolved easily in water. When this solution was made acid with acetic acid a white crystalline substance slowly separated. This was slightly soluble in hot water and difficultly soluble in hot alcohol, from which it crystallized in microscopic prisms. It decomposed with effervescence at 230° . It was very soluble in ammonia and also in an excess of hydrochloric acid. Analysis:

	Calculated for $\text{C}_7\text{H}_9\text{O}_4\text{N}_3\text{S}$.	I.	Found.	II.
N	21.10	20 95		21.04

During the above hydrolysis there was a decided odor of escaping mercaptan. In order to determine whether mercaptan could be conveniently split off by means of potassium hydroxide, another portion of 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine was heated a little longer on the steam-bath with somewhat more than 2 molecular proportions of potassium hydroxide. On acidifying the residue, a substance was obtained which did not contain sulphur and agreed in properties with cytosine-5-carboxylic acid. (Analysis III. below.)



was first prepared by evaporating the above mercaptoamino acid with concentrated hydrochloric acid on the steam-bath. After evaporating once with a moderate amount of acid, the residue was taken up in water and evaporated again to remove hydrochloric acid. It was found that the acid was almost insoluble in hot water, alcohol and acetic acid. The specimen

used for analysis was purified by dissolving in ammonia and precipitating with acetic acid. It came down in a very finely divided state and was hard to filter. It decomposed with effervescence at 256°-257°. Analysis:

	Calculated for $C_5H_5O_2N_2$.	I.	Found. II.	III.
N	27.09	27.07	27.07	26.80

To prepare this acid it is not necessary to isolate the 2-ethylmercapto-5-carboxyl-6-aminopyrimidine. The easiest way is to start with 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine and evaporate this once with an equal weight of potassium hydroxide in dilute alcohol. Concentrated hydrochloric acid is then added to the residue and the evaporation carried on again to dryness. The mixture is taken up in water, to remove potassium chloride, and, on filtering and washing with water, the acid is obtained in an almost pure condition. The aqueous solution of cytosine-5-carboxylic acid does not give a precipitate with barium chloride, picric acid or lead acetate. It gives but a slight turbidity with silver nitrate.

Action of Twenty Per Cent Sulphuric Acid: Formation of Uracil-5-carboxylic Acid. — One gram of cytosine-5-carboxylic acid was boiled on a return condenser for 20 hours with 40 cc. of sulphuric acid. A solid separated on cooling. It weighed 0.5 gram. This was crystallized from water and came down in clusters of pointed, microscopic prisms which decomposed at 277°. They were indentified as uracil-5-carboxylic acid. Analysis: 0.3133 gram substance lost 0.0329 gram water at 120°-130°.

	Calculated for $C_5H_4O_4N_2 \cdot H_2O$.	Found.
H ₂ O	10.34	10.50
N	17.94	18.22

A duplicate experiment performed as above gave 0.45 gram of uracil-5-carboxylic acid, which separated from the solution. After filtering from this, the sulphuric acid was removed and the solution concentrated to 10 cc., then precipitated with picric acid. This gave 0.17 gram picrate, crystallizing in needles, equal to 0.06 gram cytosin.

Formation of Uracil.—One half gram of cytosine-5-carbox-

ylic acid was heated with 5 cc. of 20 per cent sulphuric acid at 162° – 167° for 2 hours. On opening the sealed tube, considerable pressure was noticed and a deposit which had the appearance of uracil had separated. This was recrystallized from water and identified as uracil. Analysis:

	Calculated for $C_4H_4O_2N_2$.	Found.
N	25.00	24.97

Action of Concentrated Hydrochloric Acid: Formation of Uracil.—One gram of cytosine-5-carboxylic acid was boiled with 50 cc. of concentrated hydrochloric acid, using a return condenser, for 22 hours. The acid was then evaporated and the residue was treated with boiling water. A small portion was insoluble in hot water. This was unaltered cytosine-5-carboxylic acid; an analysis gave 26.80 per cent of nitrogen while the calculated is 27.09 per cent.

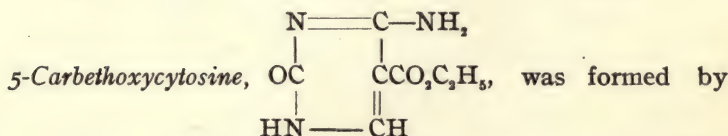
The portion which was soluble in water crystallized in balls like uracil. Analysis gave 24.90 per cent nitrogen.

Cytosine-5-carboxylic Acid Hydrochloride was prepared by crystallizing some of the acid from 20 per cent hydrochloric acid. It formed ragged pointed prisms which melted at 275° – 276° and it contained a molecule of water of crystallization.

Analysis:

0.1327 gram lost 0.0117 gram of water at 130° – 140° .

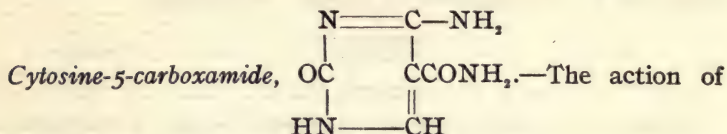
	Calculated for $C_8H_8O_3N_3.HCl.H_2O$.	Found.
H ₂ O	8.59	8.82
	Calculated for $C_8H_8O_3N_3.HCl$.	Found.
N	21.93	21.71



evaporating 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine with concentrated hydrochloric acid on the steam bath. The product was dissolved in hot water and the solution after making slightly alkaline with ammonia gave needles which

browned and decomposed slowly at about 260° – 275° . This ester was only slightly soluble in hot alcohol. Analysis:

	Calculated for $C_7H_9O_3N_3$.	I.	Found.	II.
N	22.95	22.97		23.00



concentrated aqueous ammonia on the above ester was not at all smooth. In one experiment in which the ester was heated with concentrated ammonia for 2 hours at 140° – 150° , about 25 per cent of the material remained unaltered but on evaporating the mother-liquor far more soluble material was obtained. This crystallized in tufts of hair-like needles. It was recrystallized from water. (Analysis I.) On heating, no definite melting or decomposition point was observed.

Analyses of two different samples gave the following results which show that the expected amide had been obtained.

	Calculated for $C_8H_9O_3N_4$.	I.	Found.	II.
N	36.36	35.94		35.00

NEW HAVEN, CONN.,
May, 1907.

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No. 5. November, 1907.]

CL.—RESEARCHES ON PYRIMIDINES: SYNTHESIS OF
THYMINE-5'-CARBOXYLIC ACID.

[TWENTY-SEVENTH PAPER.]

BY TREAT B. JOHNSON AND CARL FRANK SPEER.

The possibility that uracil, cytosine and thymine might be linked in nucleic acids by acid amide or polypeptide groupings was an incentive to make a thorough study of the carboxyl derivatives of these pyrimidines. Descriptions of uracil-5-carboxylic acid,¹ I., thymine-4-carboxylic acid,² IV., cytosine-5-carboxylic acid,³ III., and uracil-4-carboxylic acid,⁴

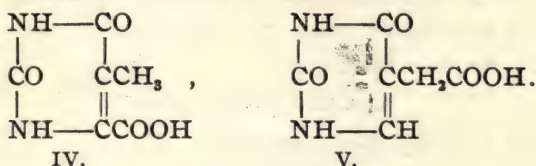
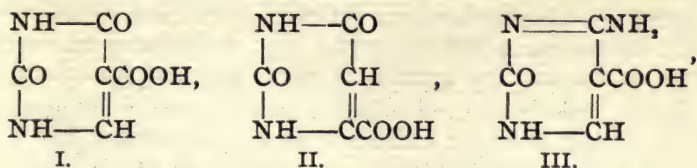
¹ Wheeler, Johnson and Johns: *THIS JOURNAL*, **37**, 392.

² Johnson: *Jour. Biolog. Chem.*, **3**, 299.

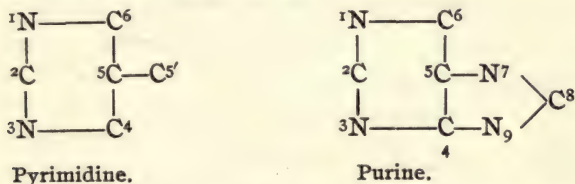
³ Wheeler and Johns: *THIS JOURNAL*, **38**, 594.

⁴ Wheeler: *Ibid.*, **38**, 358.

II., have already been published in papers from this laboratory.



We shall describe in this paper the preparation and properties of thymine-5'-carboxylic acid, V. The carbon atom in the methyl radical of thymine is designated 5' in order to avoid confusion and to distinguish from position 7 in the purine molecule. We find that this acid, V.,



can be heated with 20 per cent sulphuric acid at 160°-170° without alteration. *Thymine, therefore, cannot exist in nucleic acids as a 5'-carboxyl compound.*

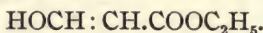
The information acquired by investigating these pyrimidine acids has advanced decidedly our knowledge of the structure of the nucleic acid molecule. The results of our work justify us in concluding that uracil is the only one of the three pyrimidines—uracil, cytosine and thymine—that can be linked in nucleic acids by an acid amide grouping—CO.NH. *Uracil might exist as a 5-carboxyl compound.* This conclusion is supported by the fact that uracil-5-carboxylic acid,¹ I., is quantitatively converted into uracil when heated with 20 per cent sulphuric acid at 160°-170°. Uracil-4-carboxylic acid,¹ II., and thymine-4-carboxylic acid,¹ IV., could be heated under

¹ Loc. cit.

the same conditions without alteration. The possibility of cytosine being linked as a 5-carboxyl compound is excluded, since cytosine-5-carboxylic acid,¹ III., is changed to uracil-5-carboxylic acid by hydrolysis with dilute sulphuric acid.

Every α -derivative of ethyl β -oxyacrylate (ethylformylacetate) that we have examined in this laboratory has condensed with a pseudothiurea, in presence of alkali, giving a 2-mercapto pyrimidine, *viz.*:

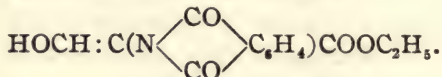
1. Ethyl β -oxyacrylate,²



2. Ethyl α -methyl- β -oxyacrylate,³



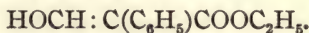
3. Ethyl α -phthalimido- β -oxyacrylate,⁴



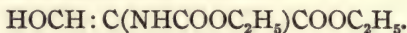
4. Ethyl α -benzoylamino- β -oxyacrylate,⁵



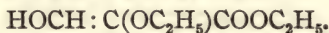
5. Ethyl α -phenyl- β -oxyacrylate,⁶



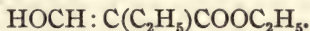
6. Ethyl α -urethane- β -oxyacrylate,⁷



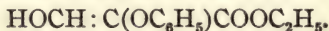
7. Ethyl α -ethoxy- β -oxyacrylate,⁸



8. Ethyl α -ethyl- β -oxyacrylate,⁹



9. Ethyl α -phenoxy- β -oxyacrylate,¹⁰



¹ *Loc. cit.*

² Wheeler and Merriam: *THIS JOURNAL*, **29**, 478.

³ Wheeler and Merriam: *Loc. cit.*

⁴ Johnson and Clapp: *THIS JOURNAL*, **32**, 130.

⁵ Johnson and Clapp: *Loc. cit.*

⁶ Wheeler and Bristol: *THIS JOURNAL*, **33**, 448.

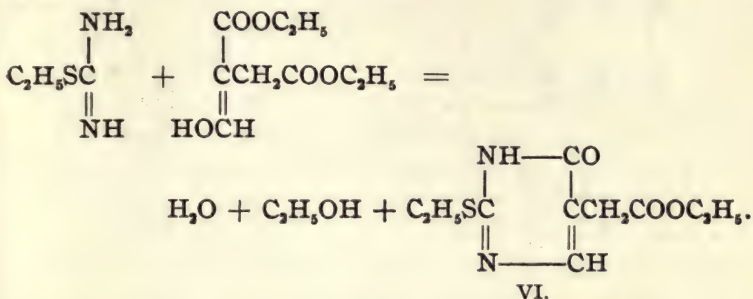
⁷ Johnson: *Ibid.*, **34**, 191.

⁸ Johnson and McCollum: *Jour. Biolog. Chem.*, **1**, 437. *THIS JOURNAL*, **36**, 149.

⁹ Johnson and Menge: *Jour. Biolog. Chem.*, **2**, 105.

¹⁰ Johnson and Heyl: *THIS JOURNAL*, **37**, 628.

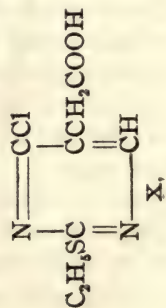
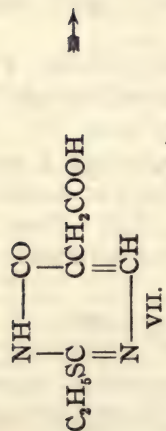
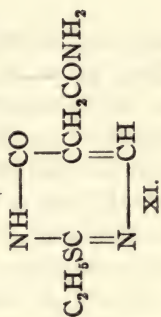
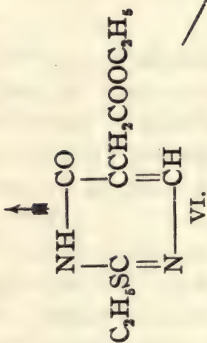
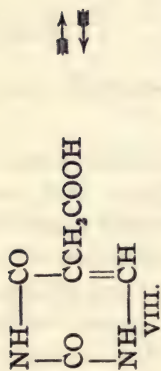
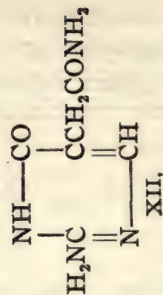
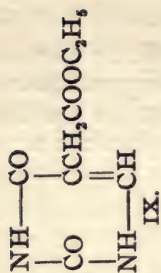
We now find that the sodium salt of diethyl formylsuccinate condenses in a smooth manner with pseudoethylthiourea, giving ethyl 2-ethylmercapto-6-oxypyrimidine-5-acetate, VI. The condensation is represented by the following equation:



When ethyl 2-ethylmercapto-6-oxypyrimidine-5-acetate, VI., was digested with concentrated hydrochloric acid, or with alcohol and hydrochloric acid, it was converted quantitatively into thymine-5'-carboxylic acid, VIII. Esterification of thymine-5'-carboxylic acid with ethyl alcohol and sulphuric acid gave thymine-5'-ethylcarboxylate, IX. 2-Ethylmercapto-6-oxypyrimidine-5-acetic acid, VII., was obtained when ethyl 2-ethylmercapto-6-oxypyrimidine-5-acetate, VI., was saponified with an alcoholic solution of potassium hydroxide. When this mercapto acid was digested with hydrochloric acid it was converted into thymine-5'-carboxylic acid.

Ethyl 2-ethylmercapto-6-oxypyrimidine-5-acetate, VI., reacts in a smooth manner with phosphorus oxychloride, giving 2-ethylmercapto-6-chlorpyrimidine-5-acetic acid, X. When the mercapto ester, VI., was heated with ammonia it was converted into 2-ethylmercapto-6-oxypyrimidine-5-acetamide, XI., and 2-amino-6-oxypyrimidine-5-acetamide, XII. These different transformations are represented by the formulas on the following page.

Thymine-5'-carboxylic acid is difficultly soluble in water and melts at about the same temperature as thymine (315°-320°). It crystallizes from water in anhydrous condition. It is a strong acid and gives an insoluble, crystalline lead salt,



when lead acetate is added to its aqueous solution. It was not precipitated by phosphotungstic acid. Addition of barium chloride to aqueous solutions of the acid produced no precipitate. Potassio-bismuth iodide gave a yellow, crystalline precipitate.

EXPERIMENTAL PART.

Diethyl Formylsuccinate, $\text{CHO} \cdot \text{CH} \cdot \text{COOC}_2\text{H}_5$.—The sodium
 $\begin{array}{c} | \\ \text{CH}_2 \cdot \text{COOC}_2\text{H}_5 \end{array}$

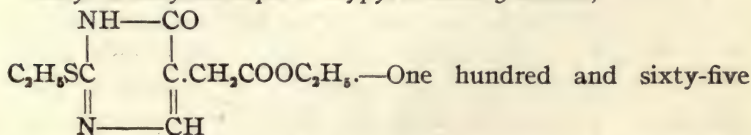
salt of this ester was prepared by condensing ethyl formate with diethyl succinate in presence of metallic sodium. Eleven grams of sodium wire were suspended in anhydrous ether and a mixture of molecular proportions of ethyl formate and diethyl succinate slowly added. There was an immediate reaction with evolution of hydrogen gas and the ether assumed a red color. The mixture was allowed to stand for ten to twelve hours and then shaken with cold water to dissolve the sodium salt of diethyl formylsuccinate. When this aqueous solution was acidified with hydrochloric acid the free ester separated as a heavy yellow oil. After drying, in ether solution with calcium chloride it was distilled under diminished pressure. The fraction that was analyzed boiled at 158° – 160° under 20 mm. pressure.

I. 0.4614 gram substance gave 0.8994 gram CO_2 and 0.2816 gram H_2O .

II. 0.5762 gram substance gave 1.1107 grams CO_2 and 0.3573 gram H_2O .

	Calculated for $\text{C}_9\text{H}_{14}\text{O}_5$.	I.	Found.	II.
C	53.4	53.16		52.58
H	6.93	6.79		6.89

Ethyl 2-Ethylmercapto-6-oxyprymidine-5-acetate,



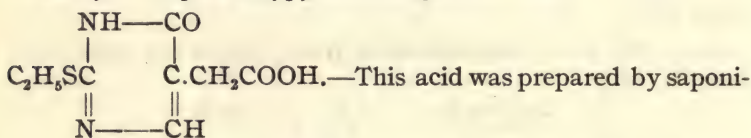
grams of diethyl succinate and one molecular proportion of ethyl formate were condensed in presence of the required

amount of metallic sodium, as described in the previous experiment. The sodium salt of diethyl formylsuccinate was then dissolved in cold water and added to an aqueous solution of 109 grams of pseudoethylthiourea hydrobromide. A molecular proportion of potassium hydroxide was then added and the mixture allowed to stand for seven to eight hours at ordinary temperature. It was then heated on the steam-bath for three hours and cooled, when prismatic crystals of the mercapto pyrimidine deposited. When the alkaline solution was acidified with acetic acid, more of the pyrimidine separated. The compound was practically insoluble in cold water, but dissolved in boiling water and separated, on cooling, in well developed, prismatic crystals. It crystallized from alcohol in slender needles melting at 146° – 147° , with no effervescence. It crystallized from water without water of crystallization. The yield of crude pyrimidine was 80 grams. Analysis (Kjeldahl):

	Calculated for $C_{10}H_{14}O_3N_2S$.	I.	Found. II.
N	11.57	11.60	11.55

In two other experiments we obtained 22 grams and 38 grams of the mercapto pyrimidine from 63 grams and 90 grams of diethyl succinate, respectively.

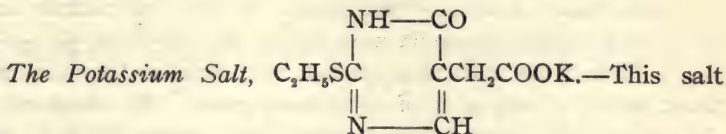
2-Ethylmercapto-6-oxyprymidine-5-acetic Acid,



fying the ethyl ester with potassium hydroxide. Ten grams of the ester and 3 grams of potassium hydroxide were digested in alcohol for about twelve hours. The alkaline solution was then evaporated to dryness and the residue obtained dissolved in warm water. This solution was then acidified with acetic acid, when about 1 gram of unaltered ester, melting at 146° , separated. After evaporating the filtrate to dryness and dissolving the residue again in a little water, the solution was acidified with a few drops of dilute hydrochloric acid. The

mercapto acid separated at once and crystallized from hot water in needles and square plates melting at 184° , with evolution of carbon dioxide and ethylmercaptan. When digested with hydrochloric acid it was converted into *thymine-5'-carboxylic acid* (see below). Analysis (Kjeldahl):

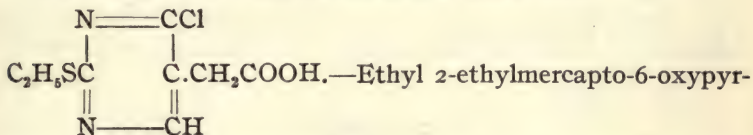
	Calculated for $C_8H_{10}O_3N_2S$.	I.	Found.	II.
N	13.08	12.9		12.85



was extremely soluble in water and alcohol. It separated from very concentrated, aqueous solutions in long needles. They did not contain water of crystallization. Analysis (Kjeldahl):

	Calculated for $C_8H_9O_3N_2SK$.	Found.
N	11.11	11.31

2-Ethylmercapto-6-chlorpyrimidine-5-acetic Acid



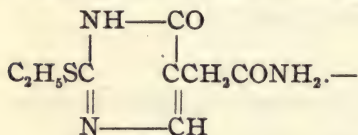
imidine-5-acetate dissolves at once in cold phosphorus oxychloride, with no evolution of heat. Fifteen grams of the pyrimidine were dissolved in 50 cc. of phosphorus oxychloride and the solution boiled gently for two and a half hours. It was then allowed to stand for five to six hours and poured upon crushed ice to destroy the excess of phosphorus halides. We obtained a dark colored solution, which was extracted several times with ether. This ether solution was then thoroughly washed with sodium hydroxide solution and the alkaline washings saved. When they were neutralized with hydrochloric acid the chlorpyrimidine separated in granular crystals. The yield was 8.5 grams. The pyrimidine was difficultly soluble

in water and very soluble in alcohol. It crystallized from alcohol in clusters of prismatic crystals, melting at 132° , to a clear oil. When heated above its melting point it decomposed with violent effervescence. Analysis (Kjeldahl):

	Calculated for $C_8H_9O_2N_2SCl$.	I.	Found. II.
N	12.07	11.9	12.02

Action of Alcoholic Ammonia on Ethyl 2-Ethylmercapto-6-oxypyrimidine-5-acetate.—Two grams of the pyrimidine and 25 cc. of alcoholic ammonia were heated for two hours at 140° – 150° . When the tube was opened there was no pressure but there was a strong odor of ethyl mercaptan. We obtained a deposit of crystalline material, which was very soluble in hot water and separated, on cooling, in prismatic crystals associated with some needles. By a fractional crystallization from water we finally separated a compound which melted at 214° , with slight effervescence. It responded to a test for sulphur and a nitrogen determination agreed with the calculated value in

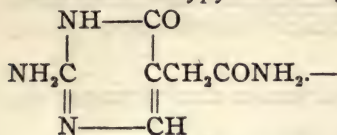
2-Ethylmercapto-6-oxypyrimidine-5-acetamide,



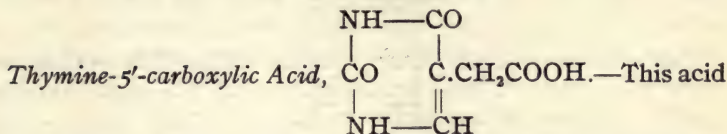
	Calculated for $C_8H_{11}O_2N_2S$.	Found.
N	19.75	19.58

In a second experiment, 4 grams of the mercapto ester and 50 cc. of alcoholic ammonia were heated for two hours at 170° – 180° . When the tube was examined there was no pressure but a strong odor of mercaptan, and small, granular crystals were suspended in the alcohol. These were removed and recrystallized from water. On cooling, prismatic crystals separated, which charred at 260° – 266° and then decomposed at about 280° , with violent effervescence. They did not respond to a test for sulphur and a nitrogen determination agreed with the calculated value in

2-Amino-6-oxypyrimidine-5-acetamide,



	Calculated for $\text{C}_6\text{H}_8\text{O}_2\text{N}_4$.	I.	Found.	II.
N	33.33	32.6		32.75



was obtained when ethyl 2-ethylmercapto-6-oxypyrimidine-5-acetate was digested in alcoholic solution with hydrochloric acid. Five grams of the mercapto ester were dissolved in a mixture of 20 cc. of alcohol and 5 cc. of concentrated hydrochloric acid and the solution heated on the steam-bath for 2.5 hours. The pyrimidine separated as a colorless, crystalline powder that was practically insoluble in alcohol. A quantitative yield of the acid was also obtained when ethyl 2-ethylmercapto-6-oxypyrimidine-5-acetate or 2-ethylmercapto-6-oxypyrimidine-5-acetic acid was digested with concentrated hydrochloric acid (Analyses IV. and V.). Analysis (Kjeldahl):

	Calculated for $\text{C}_9\text{H}_6\text{O}_4\text{N}_2$.	I.	II.	Found. III.	IV.	V.
N	16.47	16.28	16.12	16.28	16.5	16.5

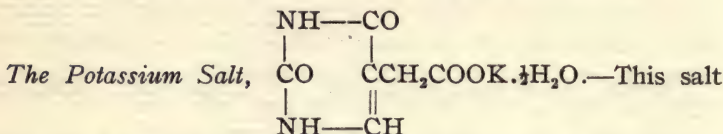
Thymine-5'-carboxylic acid was very insoluble in cold water but crystallized from boiling water in microscopic, granular crystals, which generally melted at $315^\circ - 320^\circ$, with decomposition. It did not contain water of crystallization, and when mixed with thymine the melting-point was lowered to $290^\circ - 300^\circ$. Its aqueous solution gave a strong acid reaction when tested with blue litmus. It was precipitated by silver nitrate and mercuric chloride in weak ammoniacal solutions. The silver salt dissolved in excess of ammonia. Copper carbonate was decomposed by the acid, giving an insoluble copper salt. Barium chloride does not precipitate a barium salt from

aqueous solutions of the acid. The acid was not precipitated by phosphotungstic acid, but potassio-bismuth iodide gave a yellow, granular precipitate.

Solubility in Water at 30°.—One hundred parts water dissolved

I.
0.3566 part acid

II.
0.4038 part acid



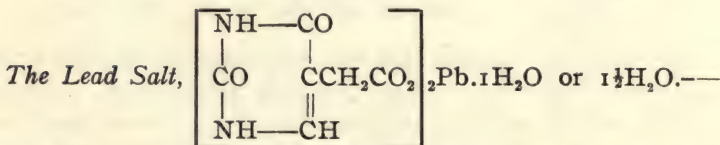
was very soluble in water and was prepared by dissolving the acid in water containing the required amount of potassium hydroxide. It crystallized from a concentrated aqueous solution in prismatic crystals containing water of crystallization. The water was determined by heating for one and a half hours at 105°–115°.

0.8947 gram substance lost 0.0307 gram H₂O.

	Calculated for C ₆ H ₅ O ₄ N ₂ K · $\frac{1}{2}$ H ₂ O.	Found.
H ₂ O	4.1	3.45

Nitrogen determination in the anhydrous salt (Kjeldahl):

	Calculated for C ₆ H ₅ O ₄ N ₂ K.	I.	Found.	II.
N	13.45	13.58		13.47



This was a very characteristic salt and separated, at once, when lead acetate was added to a hot, saturated, aqueous solution of thymine-5'-carboxylic acid. It was more insoluble than the acid and crystallized from boiling water in rhombic tables. It contained water of crystallization, which was determined by heating for two hours at 110°–115°.

0.3103 gram salt lost 0.0122 gram H₂O.

	Calculated for (C ₆ H ₅ O ₄ N ₂) ₂ Pb.H ₂ O.	Calculated for (C ₆ H ₅ O ₄ N ₂) ₂ Pb.1½H ₂ O.	Found.
H ₂ O	3.19	4.6	3.93

Nitrogen determination in the anhydrous salt (Kjeldahl):

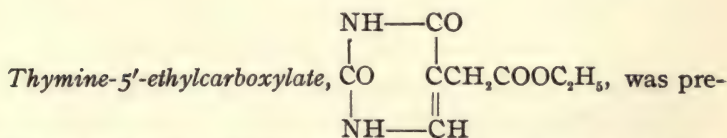
	Calculated for (C ₆ H ₅ O ₄ N ₂) ₂ Pb.	Found.
N	10.28	10.32

Action of 20 Per Cent Sulphuric Acid on Thymine-5'-carboxylic Acid.—One gram of the acid was heated with 10 cc. of sulphuric acid for two hours, at 150°–160°. There was no pressure when the tube was opened and the acid had crystallized from the acid solution in prismatic crystals. They melted at 315°–320°, with decomposition, and when mixed with thymine the decomposition point was lowered below 300°. Analysis (Kjeldahl):

	Calculated for C ₆ H ₆ O ₄ N ₂ .	I.	Found.	II.
N	16.47	16.5		16.6

In a second experiment, 3 grams of thymine-5'-carboxylic acid were heated with 30 cc. of 20 per cent sulphuric acid for ten hours, at 160°–170°. We observed practically no decomposition under these conditions and the acid was recovered unaltered, melting at 315°–320°. Analysis (Kjeldahl):

	Calculated for C ₆ H ₆ O ₄ N ₂ .	Found.
N	16.47	16.35



pared in the usual manner by esterifying the acid with absolute alcohol and concentrated sulphuric acid. It crystallized from boiling alcohol in rectangular plates melting at 204°–210°, according to the rate of heating. Analysis (Kjeldahl):

	Calculated for C ₈ H ₁₀ O ₄ N ₂ .	I.	Found.	II.
N	14.14	13.7		13.9

[Reprinted from the American Chemical Journal, Vol. XXXVIII.
No. 6. December, 1907.]

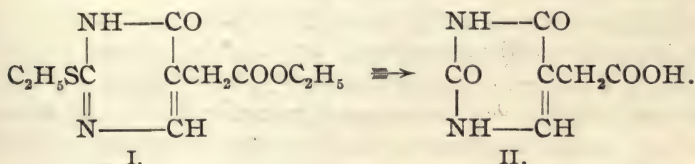
Contributions from the Sheffield Laboratory of Yale University.

CLIV.—RESEARCHES ON PYRIMIDINES: SYNTHESIS OF 4-METHYLURACIL-5-ACETIC ACID.

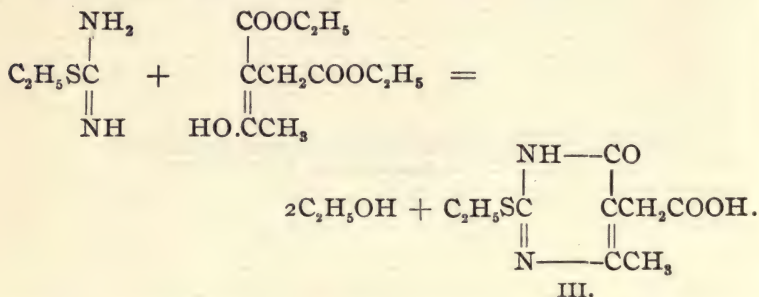
[TWENTY-EIGHTH PAPER.]

BY TREAT B. JOHNSON AND FREDERICK W. HEYL.

It was shown, in a previous paper from this laboratory,¹ that diethyl formylsuccinate condenses smoothly with pseudo-ethylthiourea, giving ethyl 2-ethylmercapto-6-oxypyrimidine-5-acetate (I.). When this pyrimidine was warmed with concentrated hydrochloric acid, it was converted quantitatively into thymine-5'-carboxylic acid (II.):



(1) 4-Methyluracil-5-acetic acid can be prepared in an analogous manner from pseudoethylthiourea and diethyl acetosuccinate.¹ They condense, in presence of an excess of alkali, giving a good yield of 2-ethylmercapto-4-methyl-6-oxypyrimidine-5-acetic acid (III.). The condensation can be represented by the following equation:



It is an interesting fact that the mercapto acid (III.) is obtained in this condensation, instead of the ethyl ester, as in the condensation with diethyl formylsuccinate.

(2) Ethylmercapto-4-methyl-6-oxypyrimidine-5-acetic acid (III.) was quantitatively converted into 4-methyluracil-5-acetic acid (VI.) when digested with concentrated hydrochloric acid. When an alcoholic solution of the mercapto acid (III.) was boiled with a small quantity of hydrochloric acid a mixture of ethyl 2-ethylmercapto-4-methyl-6-oxypyrimidine-5-acetate (IV.) and ethyl 4-methyluracil-5-acetate (V.) was obtained. The latter ester was also formed by esterifying the oxygen acid (VI.) with ethyl alcohol and sulphuric acid. 2-Amino-4-methyl-6-oxypyrimidine-5-acetic acid (VII.) was prepared by heating 2-ethylmercapto-4-methyl-6-oxypyrimidine-5-acetic acid (III.) with alcoholic ammonia.

2-Ethylmercapto-4-methyl-6-oxypyrimidine-5-acetic acid reacts smoothly with phosphorus oxychloride, giving 2-ethylmercapto-4-methyl-6-chlorpyrimidine-5-acetylchloride (VIII). This acid chloride was decomposed immediately by cold water, giving 2-ethylmercapto-4-methyl-6-chlorpyrimidine-5-acetic acid (XI). 2-Ethylmercapto-4-methyl-6-chlorpyrimidine-5-acet-

¹ Fittig and Spencer: *Ann. Chem. (Liebig)*, **283**, 67.

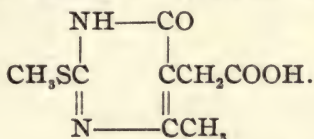
amide (IX.) was formed when the acid chloride was poured into cold alcoholic ammonia.

2-Ethylmercapto-4-methyl-6-chlorpyrimidine-5-acetic acid (XI.) is very stable in the presence of ammonia. It was recovered unaltered after heating with alcoholic ammonia at 120°. Treatment with ammonia at 135° gave 2-ethylmercapto-4-methyl-6-aminopyrimidine-5-acetic acid (XII.). When heated with alcoholic ammonia at 170°-180° the mercapto radical was also replaced by the amino group and 2,6-diamino-4-methylpyrimidine-5-acetic acid (X.) resulted. These different transformations are represented by the formulas on page 662.

4-Methyluracil-5-acetic acid (VI.) is less soluble in water than the thymine-5'-carboxylic acid (II.) described by Johnson and Speh.¹ It gives characteristic potassium, barium, and lead salts which crystallize from water with water of crystallization. The acid is not precipitated from its aqueous solution by barium chloride or phosphotungstic acid. It can be heated with 20 per cent sulphuric acid at 153°-173° without alteration.

EXPERIMENTAL PART.

2-Methylmercapto-4-methyl-6-oxypyrimidine-5-acetic Acid,

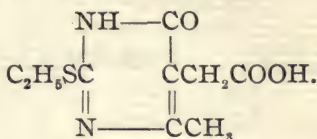


Ten grams of pseudomethylthiourea hydriodide were dissolved in water and 10 grams of diethyl acetosuccinate and 5 grams of potassium hydroxide added to the solution. The mixture was then allowed to stand for 8-10 hours at ordinary temperature and then warmed on the steam bath to complete the reaction. After cooling, the solution was acidified with hydrochloric acid, when the mercapto derivative deposited in prisms. It crystallized from hot water or alcohol in flat prisms that sintered at 260° and then decomposed at 270°-272° with effervescence. Analysis (Kjeldahl):

¹ *Loc. cit.*

	Calculated for $C_9H_{10}O_3N_2S$.	Found.	
N	13.08	I. 13.14	II. 13.06

2-Ethylmercapto-4-methyl-6-oxy-pyrimidine-5-acetic Acid,



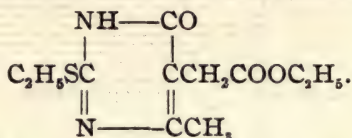
The best yield of this pyrimidine was obtained when we proceeded under the following conditions: Thirty-five grams of the hydrobromide of pseudoethylthiourea were dissolved in about 250 cc. of cold water and 43 grams of diethyl acetosuccinate stirred into the solution. Twenty-two grams of potassium hydroxide were then added, when a clear solution resulted. This was then allowed to stand overnight at ordinary temperature and finally heated on the steam bath for one hour. After cooling and shaking with ether to remove any unaltered diethyl acetosuccinate, an excess of acetic acid was added, when the mercaptopyrimidine deposited in granular, prismatic crystals. The yield was 19 grams, corresponding to about 72 per cent of the theoretical. In a second condensation we obtained 4.2 grams of the mercaptopyrimidine from 8 grams of the pseudo-urea hydrobromide and 10 grams of diethyl acetosuccinate. This pyrimidine is practically insoluble in cold, and sparingly soluble in hot, water. It deposited from boiling 95 per cent alcohol in blocks. It dissolved in boiling benzonitrile and nitrobenzene and separated from both of these solvents, on cooling, in elongated prisms. The decomposition point varies with the rate of heating, but it usually decomposed at about 255° , evolving carbon dioxide and ethylmercaptan. Analysis (Kjeldahl):

	Calculated for $C_9H_{12}O_3N_2S$.	Found.	
N	12.28	I. 12.55	II. 12.30

Potassium Salt, $C_9H_{11}O_3N_2SK$.—This salt is extremely soluble in cold water. It crystallized from 50 per cent alcohol in microscopic needles. Analysis (Kjeldahl):

	Calculated for $C_9H_{11}O_5N_2SK.$	I.	Found.	II.
N	10.52	10.67		10.45

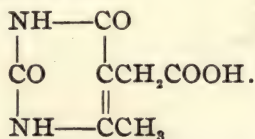
Ethyl 2-Ethylmercapto-4-methyl-6-oxypyrimidine-5-acetate,



This ester was not obtained as a product of the preceding condensation. This is explained by the fact that it was necessary to use an excess of potassium hydroxide to keep the diethyl acetosuccinate in solution and the ester, if formed, was always saponified. It was prepared by boiling the mercapto acid in alcoholic solution with a few drops of sulphuric acid. Two grams of the mercapto acid, 25 cc. of absolute alcohol, and 2 cc. of concentrated sulphuric acid were digested on the steam bath for 5 hours. The excess of alcohol was then evaporated at ordinary temperature, when we obtained an oily residue with some colorless, prismatic crystals in suspension. These were filtered by suction and the syrup again allowed to stand for a few hours, when a second crop was obtained. The yield was 0.25 gram and the compound was identified as 4-methyluracil-5-ethylacetate (see below). The syrup was treated with 20-30 cc. of cold water, when a crystalline compound deposited which melted at 151° - 163° to a clear oil. It deposited from 95 per cent alcohol in hairlike crystals that melted at 163° - 165° to a clear oil. It gave a test for sulphur. Analysis (Kjeldahl):

	Calculated for $C_{11}H_{13}O_5N_2S.$	I.	Found.	II.
N	10.93	11.4		11.08

4-Methyluracil-5-acetic Acid,



2-Ethylmercapto-4-methyl-6-oxypyrimidine-5-acetic acid dissolves at once in cold, concentrated hydrochloric acid and the

solution can be evaporated to dryness on the steam bath and the acid recovered unaltered. A quantitative yield of the oxygen acid was obtained, nevertheless, by boiling the mercaptopyrimidine with concentrated hydrochloric acid until the evolution of ethylmercaptan ceased. It deposited from the boiling acid solution as a heavy, granular powder. The acid is practically insoluble in boiling alcohol and insoluble in cold water. It crystallized from hot water in long, transparent prisms that sintered at about 329° and decomposed at 340° (Anschütz thermometer) with violent effervescence. Bromine does not react with the acid in acetic acid solution at ordinary temperature. Analysis:

I. 0.1950 gram of substance gave 0.3274 gram of CO_2 and 0.0787 gram of H_2O .

II. 0.2352 gram of substance gave 0.3935 gram of CO_2 and 0.0955 gram of H_2O . Nitrogen (Kjeldahl):

	Calculated for $\text{C}_7\text{H}_8\text{O}_4\text{N}_2$.	I.	Found. II.	III.	IV.
C	45.65	45.77	45.62		
H	4.34	4.48	4.50		
N	15.21			15.09	15.10

Solubility in Water at 25° .—One hundred grams of water dissolved:

I.	II.
0.0901 gram acid	0.0894 gram acid

Potassium Salt of 4-Methyluracil-5-acetic Acid, $\text{C}_7\text{H}_7\text{O}_4\text{N}_2\text{K} \cdot 3\text{H}_2\text{O}$, was prepared by dissolving the acid in water with one molecular proportion of potassium hydroxide. The salt was extremely soluble in water but crystallized from very concentrated solutions in prismatic crystals. They contained water of crystallization which was determined by heating the salt at 105° – 125° for 5 hours.

0.8455 gram of the salt lost 0.1544 gram H_2O .

	Calculated for $\text{C}_7\text{H}_7\text{O}_4\text{N}_2\text{K} \cdot 3\text{H}_2\text{O}$.	Found.
H_2O	19.5	18.26

Nitrogen determination for anhydrous salt (Kjeldahl):

	Calculated for $\text{C}_7\text{H}_7\text{O}_4\text{N}_2\text{K}$.	Found.
N	12.60	12.42

Silver Salt of 4-Methyluracil-5-acetic Acid, $C_7H_7O_4N_2Ag$.—When the potassium salt described above was dissolved in water and a molecular proportion of silver nitrate added, a gelatinous silver salt deposited. It was insoluble in boiling water and did not assume a crystalline form. Analysis for silver:

	Calculated for $C_7H_7O_4N_2Ag$.	Found.
Ag	37.11	40.00

Barium Salt of 4-Methyluracil-5-acetic Acid, $(C_7H_7O_4N_2)_2Ba.H_2O$.—When the calculated proportions of the acid and barium chloride were dissolved in hot water and the solution cooled, the unaltered acid separated. The salt was prepared by dissolving the potassium salt in water and adding the calculated amount of barium chloride. The salt separated, on cooling, in small prisms which were dried for analysis in a desiccator over sulphuric acid. It contained one molecule of water of crystallization which was determined by heating for 2 hours at 110° – 136° .

0.8114 gram of salt lost 0.0300 gram of H_2O .

	Calculated for $(C_7H_7O_4N_2)_2Ba.H_2O$.	Found.
H_2O	3.45	3.69

Nitrogen determination for anhydrous salt (Kjeldahl):

	Calculated for $(C_7H_7O_4N_2)_2Ba$.	Found.
N	11.12	11.05

Lead Salt of 4-Methyluracil-5-acetic Acid, $(C_7H_7O_4N_2)_2Pb.H_2O$.—This salt was obtained as an insoluble crystalline powder when lead acetate was added to a solution of the acid. It crystallized from water in glistening plates or flat prisms which were dried for analysis in a desiccator over sulphuric acid. It contained one molecule of water of crystallization which was determined by heating at 117° – 125° for 4 hours.

1.2847 grams of salt lost 0.0377 gram H_2O .

	Calculated for $(C_7H_7O_4N_2)_2Pb.H_2O$.	Found.
H_2O	3.04	2.93

Analysis of the anhydrous salt:

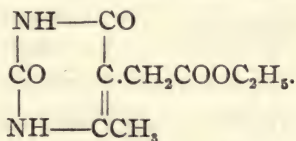
0.2594 gram substance gave 0.2769 gram CO_2 and 0.0583 gram H_2O . Nitrogen (Kjeldahl):

	Calculated for ($\text{C}_7\text{H}_7\text{O}_4\text{N}_2$) ₂ Pb.	I.	Found. II.	III.
C	29.32	29.12		
H	2.44	2.49		
N	9.77		10.00	9.73

Action of 20 Per Cent Sulphuric Acid.—The acid was recovered unaltered after heating with sulphuric acid for 2 hours at 153° – 173° . When crystallized from water it decomposed at 340° . Analysis (Kjeldahl):

	Calculated for $\text{C}_7\text{H}_5\text{O}_4\text{N}_2$.	I.	Found II.	III.
N	15.21	15.31	15.32	15.17

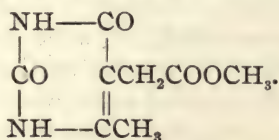
Ethyl Ester of 4-Methyluracil-5-acetic Acid,



This ester was obtained as a secondary product when we esterified 2-ethylmercapto-4-methyl-6-oxypyrimidine-5-acetic acid. It was easily obtained in pure condition by esterifying the oxygen acid in the usual manner. It crystallized from 95 per cent alcohol in needles that melted at 221° – 222° to a clear oil. Analysis (Kjeldahl):

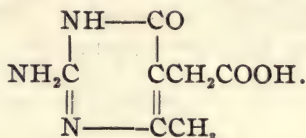
	Calculated for $\text{C}_9\text{H}_{12}\text{O}_4\text{N}_2$.	Found.
N	13.20	13.12

Methyl Ester of 4-Methyluracil-5-acetic Acid,



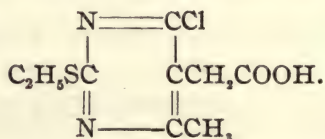
This ester deposited from methyl alcohol in fine needles that decomposed at 280° – 282° . Analysis (Kjeldahl):

	Calculated for $C_8H_{10}O_4N_2$.	I.	Found.	II.
N	14.14	14.10		14.4

2-Amino-4-methyl-6-oxypyrimidine-5-acetic Acid,

Four grams of 2-ethylmercapto-4-methyl-6-oxypyrimidine-5-acetic acid were heated with alcoholic ammonia for 4 hours at 170° – 180° . When the tube was opened there was some pressure, and the odor of ethylmercaptan was apparent. The solution was evaporated to dryness and the crystalline residue purified by recrystallization from water. It deposited in needles that decomposed at 322° with effervescence. Analysis (Kjeldahl):

	Calculated for $C_7H_9O_3N_3$.	I.	Found.	II.
N	22.95	23.3		23.2

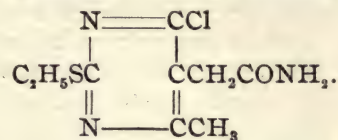
2-Ethylmercapto-4-methyl-6-chlorpyrimidine-5-acetic Acid,

Ten grams of 2-ethylmercapto-4-methyl-6-oxypyrimidine-5-acetic acid and 50 cc. of phosphorus oxychloride were warmed on the steam bath until the evolution of hydrochloric acid gas practically ceased (2 hours). A dark colored solution was obtained. This was slowly poured upon crushed ice to decompose the excess of phosphorus oxychloride. No insoluble material deposited after this treatment, but when the acid solution was neutralized with sodium hydroxide the chloride separated in slender needles which dissolved again when an excess of alkali was added. The chloride was soluble in boiling benzene but insoluble in cold benzene; very soluble in alcohol. It was purified for analysis by recrystallization from hot water and depos-

ited in needles that melted at 118°–119° with evolution of carbon dioxide. The yield was good. Analysis (Kjeldahl):

	Calculated for $C_9H_{11}O_2N_3SCl$.		Found.
N	11.35	11.53	II. 56

2-Ethylmercapto-4-methyl-6-chlorpyrimidine-5-acetamide,

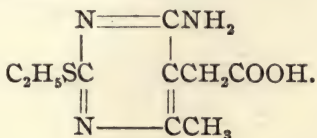


2-Ethylmercapto-4-methyl-6-oxypyrimidine-5-acetic acid was digested with an excess of phosphorus oxychloride until the evolution of hydrochloric acid gas ceased. Instead of being poured into water as in the previous experiment, this solution was poured slowly into a large volume of cold, alcoholic ammonia. The excess of alcohol and ammonia was then evaporated and the residue triturated with cold water to dissolve ammonium chloride. We obtained a crystalline compound that was insoluble in cold water but crystallized from hot water in sheaves that decomposed at 167°. The compound was very soluble in hot alcohol but can be crystallized from 50 per cent alcohol and from benzene. It was insoluble in dilute sodium hydroxide solution. Analysis (Kjeldahl):

	Calculated for $C_9H_{12}ON_3SCl$.	I.	Found.
N	17.10	17.5	II. 17.4

Action of Alcoholic Ammonia on 2-Ethylmercapto-4-methyl-6-chlorpyrimidine-5-acetic Acid.—The mercaptopyrimidine was recovered unaltered after heating with strong, alcoholic ammonia for 2 hours at 85°–95° and again for 3 hours at 110°–120°.

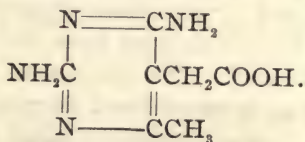
Action at 125°–135°: Formation of 2-Ethylmercapto-4-methyl-6-aminopyrimidine-5-acetic Acid,



Two and five-tenths grams of the chloride were heated with alcoholic ammonia for 2.5 hours at 125°–135°. When the tube was opened there was some pressure and a small amount of colorless, crystalline material was suspended in the alcohol. This was identified as the ammonium salt of 2-ethylmercapto-4-methyl-6-aminopyrimidine-5-acetic acid. The free acid was obtained by triturating the salt with dilute acetic acid. It deposited from 95 per cent alcohol in beautiful needles that melted sharply at 221°. They gave tests for sulphur and chlorine. This reaction was not smooth and the yield of the amino derivative was poor. When the alcoholic filtrates were evaporated to dryness a crystalline residue deposited. This proved to be a mixture from which nothing sufficiently pure for analysis was isolated. Analysis (Kjeldahl):

	Calculated for $C_9H_{13}O_2N_3S$.	Found.
N	18.50	18.64

2,6-Diamino-4-methylpyrimidine-5-acetic Acid,



This base was prepared by heating 2-ethylmercapto-4-methyl-6-chlorpyrimidine-5-acetic acid with alcoholic ammonia for 2 hours at 167°–180°. When the tube was opened there was much pressure, and a crystalline compound had deposited from the alcohol. This crystallized from hot water in small prismatic crystals that melted at 279°–280° with effervescence, turning brown at about 270°. It did not give tests for sulphur and chlorine, and dissolved in alkali and acids. Analysis (Kjeldahl):

	Calculated for $C_7H_{10}O_2N_4$.	Found.
N	30.77	30.61

NEW HAVEN, CONN.,
July 6, 1907.

VIII. RESEARCHES ON PYRIMIDINS: A METHOD OF SEPARATING THYMIN FROM URACIL.

(Twenty-ninth Paper.)

By TREAT B. JOHNSON.

(*From the Sheffield Laboratory of Yale University.*)

(Received for publication, March 28, 1908).

New data about the cleavage products of nucleic acids contribute to our knowledge of the constitution of these acids. Practical analytical methods for the quantitative determination of the products of hydrolysis are of the greatest importance. Kossel and his co-workers have developed excellent methods for determining the purin bases—xanthin, guanin, adenin and hypoxanthin. On the other hand, methods for separating quantitatively the pyrimidins are lacking. A delicate qualitative test for uracil and cytosin, in presence of thymin, has been described in a publication from this laboratory,¹ but at present there is no test, or characteristic derivative known, which serves for the identification of thymin in presence of uracil. For its detection we make use of the sublimation, the behavior towards silver nitrate and its elementary analysis.

A careful review of the nucleic acid literature reveals the fact that several investigations, in this field, signify the necessity of a practical method of separating thymin from uracil. Kutscher² in an investigation on the autolysis of thymus glands isolated 0.6 gram of a crystalline substance whose properties corresponded with those of thymin, but whose content of nitrogen did not agree with the theoretical value. He found 23.4 and 24.1 per cent of nitrogen while the calculated value for thymin is 22.22 per cent. His views are summarized in his own words: "Diese Reactionen der Krystalle sowie ihr Verhalten gegen ammoniakalische Silberlösung sprachen für Thymin, doch

¹ Wheeler and Johnson: *This Journal*, iii, p. 183.

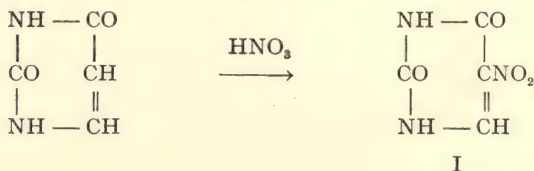
² *Zeitschr. f. physiol. Chem.*, xxxiv, p. 114.

bestätigte die Analyse diese Voraussetzung nicht völlig. Auch durch vielfache Umkrystallization und andere Reinigungsversuche liess sich dieser Stickstoffwerth nicht herunterdrücken. Es musste also dem Thymin eine stickstoff reichere Substanz vielleicht Uracil beigemenget sein."

Steudel¹ in an investigation on the hydrolysis of thymus nucleic acid with hydriodic acid isolated 5.9330 grams of a substance which gave 23.38 per cent of nitrogen on analysis. He says: "Als die Flüssigkeit jetzt eingeeengt wurde, schied sich ein Gemenge von Thymin und Uracil aus, das ich in Ermangelung einer guten Trennungsmethode nicht weiter aufgeteilt, sondern als solches analysiert habe." He² also obtained a mixture of thymin and uracil in a later investigation on the oxidation of nucleic acid with nitric acid. In a recent paper, entitled "Die Zusammensetzung der Nucleinsäuren aus Thymus und aus Heringssperma," Steudel³ wrote: "Der nach der Krystallization der alloxurbasen noch bleibende Rest lieferte weiterer Behandlung Thymin und Uracil. Diese beiden Körper liessen sich durch fraktionierte Krystallization zwar nicht quantitativ aber doch qualitativ gut trennen."

I shall describe in this paper a new, characteristic derivative of thymin, and a method of separating, practically quantitatively thymin from uracil.

Uracil and thymin do not react, below 100°, with nitric acid of density 1.41. On the other hand uracil dissolves, at ordinary temperature, in fuming nitric acid of density 1.5 giving practically a quantitative yield of 5-nitrouracil I. Thymin reacts, under the same conditions, giving a quantitative yield of the addition product—oxynitrohydrothymin⁴ II.

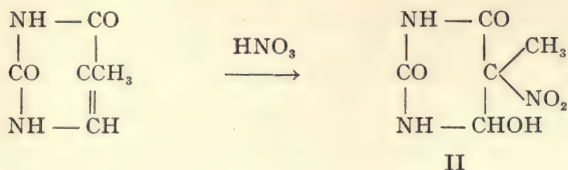


¹ *Zeitschr. f. physiol Chem.*, xlii, p. 169.

² *Ibid.*, xlviii, p. 425.

³ *Ibid.*, liii, p. 14.

⁴ Johnson: *Amer. Chem. Journ.* (To be published in vol. xl.)



In a paper, entitled "Die Constitution des Thymins,"¹ Steudel has described the action of concentrated nitric acid on thymin. He obtained a compound to which he assigned the empirical formula, $\text{C}_4\text{H}_4\text{O}_3\text{N}_4$. He gave no melting point for the compound, but states that it did not contain water of crystallization; that it was soluble in warm water and ammonia and gave, on reduction, a derivative which responded to Weidel's alloxan reaction. The data which I have obtained² seem to indicate that Steudel's *nitrothymin* was a secondary decomposition product and not a simple thymin derivative.

The formation of the hydropyrimidin II, involves a direct addition of nitric acid to the double bond between the four and five positions of the pyrimidin ring. Oxynitrohydrothymin II, exists in two modifications which I have designated by the Greek letters α and β . The two isomers are formed under practically the same conditions. The α -derivative is the stable modification and melts at 183° to 185° . The β -derivative melts at 230° to 235° and rearranges to the α -form at the ordinary temperature. These isomeric oxynitrohydrothymins are especially characterized by their crystalline habit, and are converted quantitatively into thymin by reduction with tin and hydrochloric acid.

5-Nitouracil and oxynitrohydrothymin show a remarkable difference in solubility in cold, absolute ethyl alcohol. The hydropyrimidin is extremely soluble in this reagent, while 5-nitouracil requires approximately 800 to 900 parts of cold alcohol for complete solution. I have devised a simple method of separating thymin from uracil by the use of this difference in solubility in alcohol. The mixture of uracil and thymin is treated with the proper proportions of fuming nitric acid (sp. gr. 1.5) and converted into 5-nitouracil and oxynitrohydrothymin respectively.

¹ *Zeitschr. f. physiol. Chem.*, xxxii, p. 241.

² *Loc. cit.*

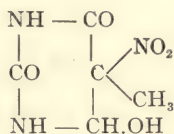
The conditions of this operation are described in detail in the experimental part of this paper. The hydrothymin is then separated from nitrouracil by trituration with absolute alcohol. The hydrothymin can be identified by its melting point and crystalline habit. Furthermore the thymin can be recovered by reduction of the hydropyrimidin with tin and hydrochloric acid. The nitrouracil is identified by elementary analysis and reduction to 5-aminouracil¹ with aluminum amalgam. This base gives a characteristic picrate which melts at 247°.²

The Action of Nitric Acid on Thymin.

Nitric Acid (sp. gr. 1.415): Five-tenths of a gram of thymin was dissolved in 2 cc. of concentrated nitric acid and the solution evaporated to dryness on the steam bath. There was no evidence of any reaction and the thymin was recovered unaltered. It deposited from hot water in plates that decomposed at about 321°. When mixed with pure thymin this decomposition point was not lowered. Analysis (Kjeldahl):

	Calculated for C ₅ H ₆ O ₂ N ₂ :	Found:
N.....	22.22	22.33

Nitric Acid (sp. gr. 1.5): *The Formation of α-Oxynitrohydrothymin:*



Thymin dissolves in cold, fuming nitric acid with slight evolution of heat. If red fumes are evolved by this treatment it is an indication that the thymin is not pure. The hydropyrimidin was obtained perfectly pure, and the yield was quantitative, when thymin was treated with fuming nitric acid under the following conditions: One gram of thymin was dissolved in 6 cc. of nitric acid and the solution allowed to evaporate at ordinary temperature. The nitropyrimidin deposited in large, well-de-

¹ Behrend and Grünwald: *Ann. d. Chem.*, cccix, p. 256.

² Wheeler and Bristol: *Amer. Chem. Journ.*, xxxiii, p. 437.

veloped prisms or blocks (see figure) which decrepitated above 130° and melted at 183° with violent effervescence. The compound was soluble in hot water, extremely soluble in alcohol, and separated from both these solvents in blocks that melted at 183° to 185° . It was insoluble in benzene. The pyrimidin did not lose weight after drying for 1.5 hours at 100° to 110° and again for one-half hour at 110° to 115° . When heated above 120° it slowly underwent decomposition. The composition of the compound was not altered by recrystallization from absolute alcohol (Analysis III):

0.2086 gram substance gave 0.2454 gram CO_2 and 0.0695 gram H_2O . Nitrogen determinations (Kjeldahl):

	Calculated for $\text{C}_5\text{H}_7\text{O}_5\text{N}_3$:	Calculated for $\text{C}_5\text{H}_6\text{O}_2\text{N}_2$ (Thymin):	I.	Found: II.	III.
C.....	31.74	47.61	32.08		
H.....	3.70	4.76	3.70		
N.....	22.22	22.22		22.00	21.95

α -Oxynitrohydrothymin dissolves in water giving an acid reaction. The pyrimidin undergoes decomposition when its aqueous solution is boiled. The addition of barium hydroxide to its aqueous solution produces no precipitate or color. No thymin deposited when an alcoholic solution of the pyrimidin was treated with ammonia. When the nitropyrimidin was dissolved in concentrated sulphuric acid, and a few drops of ferrous sulphate solution added, the characteristic test for nitric acid was obtained.

α -Oxynitrohydrothymin can also be prepared by dissolving thymin in fuming nitric acid (1.5) and evaporating the solution to dryness, at once, on the steam bath. This method of nitration can be recommended for preparing quickly small quantities of the hydropyrimidin. The yields are not quantitative since part of the thymin undergoes oxidation. The best results are obtained by this method, when 1 gram portions of thymin are nitrated under the following conditions: One gram of thymin is dissolved in 4 cc. of nitric acid (1.5) and the solution evaporated to dryness, at 100° , as quickly as possible. The nitrothymin is obtained as a colorless, crystalline residue which crystallizes from water in blocks decomposing at 183° to 185° . It is possible, in this manner, to prepare several grams of the hydropyrimidin

in a few minutes. The yields obtained by this method of nitration were very unifrom and are given in the table below:

	Nitric acid. sp. gr. 1.5	Weight of thymin.	Weight of crude oxynitrohydro- thymin.	Weight of hydropyrimidin after crystalliza- tion from water.	Percentage of theoretical.
	cc.	grams.	grams.	gram.	per cent.
1	4	1.0	1.1	0.80	57.1
2	4	1.	1.1	0.82	58.5
3	4	1.	1.1	0.79	56.4
4	4	1.	1.1	0.81	57.8
5	8	2.	2.15	1.60	55.5
6	4	1.	1.2	0.90	64.4
7	8	2.	2.1	1.50	53.5

Crystallography of Oxynitrohydrothymin by W. E. Ford.

The pyrimidin crystallizes in the triclinic system, showing a combination of b (010), c (001), a (100), M (110), d (034) and x (111). The crystals were small, averaging about 2 mm. broad by 1 mm. thick. In habit they present the appearance of diamond shaped tables with beveled edges, as is illustrated in the

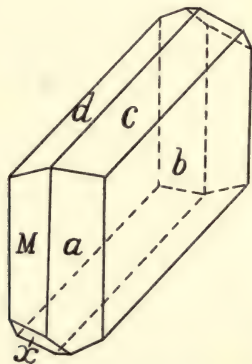


figure. The face b (010) is always the most prominent, while the prism with the pinacoid a , and the base with the dome d form the beveling faces. Frequently one of these latter faces is much subordinated in size, or may be entirely wanting. The negative pyramid x is always small and often not present. The crystal

faces, although distinct to the eye, were very poorly adapted for measurement with the reflection goniometer. They were usually quite rough or curved and gave indistinct and broad signals on the goniometer. A series of the crystals were measured on the two circle goniometer and the average of the best readings obtained were taken for the fundamental angles, but the angles as given and the crystallographic constants calculated from them can be considered only as approximate. The measured angles were as follows:

$$(010) : (110) = 63^{\circ} 54'.$$

$$(010) : (100) = 96^{\circ} 15'.$$

$$(010) : (001) = 73^{\circ} 38'.$$

$$\text{Zone } (010).(110) : \text{zone } (010).(001) = 79^{\circ} 35'.$$

$$\text{Zone } (010).(110) : \text{zone } (010).(101) = 50^{\circ} 5'.$$

$$(010) : (034) = 71^{\circ} 33'; \text{ calc.} = 71^{\circ} 46'.$$

Using the first five measurements as fundamentals the crystal constants were calculated to be:

$$a:b:c = 0.578 : 1.000 : 0.420. \alpha = 107^{\circ} 35', \beta = 100^{\circ} 25', \gamma = 80^{\circ} 59'.$$

The crystals show a good cleavage parallel to c (001). On account of the nature of the material only a few of the optical facts concerning the compound could be determined. It possesses a strong double refraction. The extinction direction on b (010) is inclined to the edge between b and a at 31° . The crystals when looked at in the polariscope in a direction perpendicular to c (001), the cleavage face, show the emergence of an optic axis nearly in the center of the field.

Reduction of α -Oxynitrohydrothymine with Aluminum-Amalgam.

Two and five-tenths grams of the hydropyrimidin were dissolved in cold water and reduced for 1.5 hours with an excess of aluminium-amalgam. The temperature was not allowed to rise above 40° during the reduction. After filtering from aluminium-amalgam and aluminium hydroxide the filtrate was evaporated to dryness. I obtained a crystalline deposit which was difficultly soluble in cold water, but separated from hot water in plates melting at 320° . When mixed with thymine the melting point

was not lowered. It dissolved in fuming nitric acid giving the original α -oxynitrohydrothymin melting at 183° to 185° .

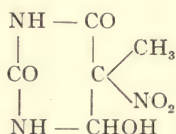
	Calculated for $C_5H_6O_2N_2$:	Found:
N	22.22	22.01

Reduction of α -Oxynitrohydrothymin with Tin and Hydrochloric Acid.

Two and two-tenths grams of the pyrimidin were reduced for one hour with an excess of tin and concentrated hydrochloric acid. The acid solution was then evaporated to dryness, the residue dissolved in water, and the tin removed by precipitation with hydrogen sulphide. When the aqueous filtrate was concentrated and cooled, thymin separated in glistening plates which decomposed at 320° . Analysis (Kjeldahl):

	Calculated for $C_5H_6O_2N_2$:	Found:
N	22.22	22.10

β -Oxynitrohydrothymin:



I have performed fifteen experiments, during this research, to determine the behavior of fuming nitric acid towards thymin under different conditions. I have taken different amounts of thymin (0.5 to 5.0 grams) and have varied the proportions of nitric acid. I have also allowed the acid solutions to evaporate under different conditions—at room temperature, on the steam oven, in a vacuum over sulphuric acid and at 100° —but in only two experiments have I observed the formation of β -oxynitrohydrothymin. The conditions, under which I obtained this isomer were as follows: One and six-tenths grams of thymin were dissolved in 8 cc. of cold, fuming nitric acid (1.5) and the solution allowed to evaporate, in the air, over night. The next morning large, transparent blocks had deposited which showed no signs of melting at 183° to 185° but decomposed at 230° to

235° according to the rate of heating. One of the crystals selected for analysis weighed 0.2600 gram. The isomer did not revert to the α -derivative when crystallized from water or absolute alcohol, but separated on cooling in well developed prisms decomposing at 230° to 236°. In another experiment 0.5 gram of thymin was dissolved in 10 cc. of fuming nitric acid and the solution allowed to evaporate over sulphuric acid, in a vacuum desiccator. I obtained practically a quantitative yield of the β -derivative melting at 230° to 235°. The compound did not lose weight when heated for one-half hour at 90° to 100°. Analyses (Kjeldahl):

	Calculated for	Found:	
	$C_5H_7O_5N_3$:	I.	II.
N	22.22	22.00	22.1

Reduction of β -Oxynitrohydrothymin with Tin and Hydrochloric Acid.

This compound was reduced in the same manner as the α -derivative. The excess of tin was removed with hydrogen sulphide and the filtrate evaporated to dryness. I obtained a crystalline residue which separated from water in plates melting at 315° to 320°. The compound sublimed when heated in a test-tube and when mixed with thymin the melting point was not lowered. It dissolved in fuming nitric acid giving α -oxynitrohydrothymin melting at 183° to 185°. Analysis (Kjeldahl):

	Calculated for	Found:
	$C_8H_6O_2N_2$:	
N	22.22	22.31

Rearrangement of β -Oxynitrohydrothymin into α -Oxynitrohydrothymin.

Some of the α -pyrimidin, melting at 183° to 185°, was preserved in a desiccator from May 29, 1907, until January 17, 1908. It apparently underwent no change and melted at 181° to 183° with effervescence. A sample of the β -pyrimidin, melting at 230° to 235° was preserved from June 19, 1907, to October 7, 1907. It then decomposed at 227° to 235°, and a nitrogen determination (Kjeldahl) gave 22 per cent nitrogen; calculated 22.22 per cent. This material was not examined again until January

16, 1908. It then had completely rearranged to the α -pyrimidin and melted at 183° to 188° with effervescence. A mixture of this material and pure α -oxynitrohydrothymin melted 183° to 186° . Analysis (Kjeldahl):

	Calculated for $C_5H_7O_5N_3$:	Found:
N.....	22.22	21.9

Method of Analysis.

The mixture of thymin and uracil, which is to be analyzed, is dried at 100° , then pulverized finely, and dissolved, at ordinary temperature (20°), in fuming nitric acid. It is essential for the success of this separation that the nitric acid have a density of 1.5 and that enough be taken to react with all the uracil and thymin present. It has been my experience that the best proportions are about 10 cc. of fuming nitric acid for 1 gram of the pyrimidin mixture. The operation is performed best in a glass, crystallizing dish of about 5.5 cm. diameter, when working with 1 gram portions.

When the pyrimidins have completely dissolved the solution is evaporated to complete dryness at a temperature of 50° to 60° . If impurities are present, which are oxidized by nitric acid at this temperature, the excess of acid can be removed by drying in a vacuum over sulphuric acid and potash. The mixture of nitrouracil and oxynitrohydrothymin is then pulverized in a mortar and triturated thoroughly with cold, absolute alcohol, using 15 cc. of alcohol for each gram of the original mixture. The insoluble nitrouracil is filtered off with suction, washed with 5 cc. of cold alcohol and purified by recrystallization from hot alcohol or water. It is identified in the manner described above.

In order to obtain the oxynitrohydrothymin the alcohol washings are allowed to evaporate spontaneously in a good draught. It is not advisable to remove the alcohol by heating on the steam bath. After removal of the alcohol the oxynitrohydrothymin is recrystallized from the least possible quantity of hot water and identified by its characteristic melting point and crystalline habit.

The results of the analyses of three different mixtures of uracil and thymin are given in the following table:

Pyrimidins.	HNO ₃ (1.5).	Nitrouracil insoluble in alcohol.	Calculated	Oxynitrohydrothymine soluble in alcohol.	Calculated	Total weight of nitrouracil and oxynitro- hydrothymine found.	Theoretical weight.
<i>gram.</i> I. 0.5 uracil. 0.5 thymine.	<i>cc.</i> 5.0	<i>gram.</i> 0.61 (No test for uracil)	<i>gram.</i> 0.70	<i>gram.</i> 0.83 m. p. after first crystal- lization, 180°-182°.	<i>gram.</i> 0.75	<i>gram.</i> 1.44	<i>gram.</i> 1.45
II. 0.2 uracil 0.2 thymine.	2.0	0.25 (No test for uracil)	0.28	0.30 m. p. after first crystal- lization, 180°-184°.	0.30	0.55	0.58
III. 1.0 uracil 0.2 thymine	10	1.32 (No test for uracil)	1.40	0.24 m. p. after first crystal- lization, 183°. Nitrogen (Kjeldahl) = 21.9. Theoretical = 22.22.	0.30	1.56	1.70

I take pleasure in thanking Professor Ford for the crystallographic description of oxynitrohydrothymin.

CLVI. RESEARCHES ON PYRIMIDINES. THE ACTION
OF NITRIC ACID ON 2,6-DIOXYPYRIMIDINES.
OXYNITROHYDROTHYMINE.

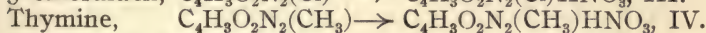
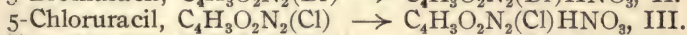
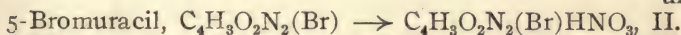
[THIRTIETH PAPER.]

BY TREAT B. JOHNSON.

I shall describe, in this paper, some results which I have obtained by examining the behavior of fuming nitric acid towards 5-bromuracil, 5-chloruracil, and synthetical thymine.

In a paper entitled "Die Constitution des Thymins,"¹ Steudel has described the action of concentrated nitric acid on thymine. He obtained a compound to which he assigned the empirical formula $C_4H_4O_3N_4$. He gave no melting point for the compound, but states that it did not contain water of crystallization, that it was soluble in warm water and ammonia, and gave, on reduction, a derivative which responded to Weidel's alloxan reaction. I have repeated Steudel's experiment and have investigated the action of nitric acid of different concentrations and under various conditions, but in no case have I obtained a compound identical with his *nitrothymine*. The data which I have obtained seem to indicate that Steudel's *nitrothymine* was a secondary decomposition product, and not a simple thymine derivative.

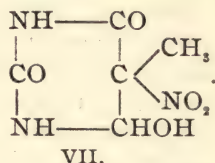
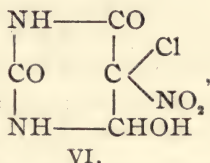
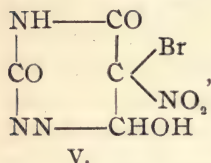
Uracil, 5-bromuracil, 5-chloruracil, and thymine do not react, below 100° , with nitric acid of density 1.41. On the other hand, uracil dissolves, at ordinary temperature, in fuming nitric acid (sp. gr. 1.5), giving a good yield of 5-nitrouracil (I.). 5-Bromuracil, 5-chloruracil, and thymine react, under the same conditions, giving three derivatives corresponding to the empirical formulas II., III., and IV., respectively. The same compound IV. was also obtained when thymine was treated with concentrated nitric acid according to the directions of Steudel.²



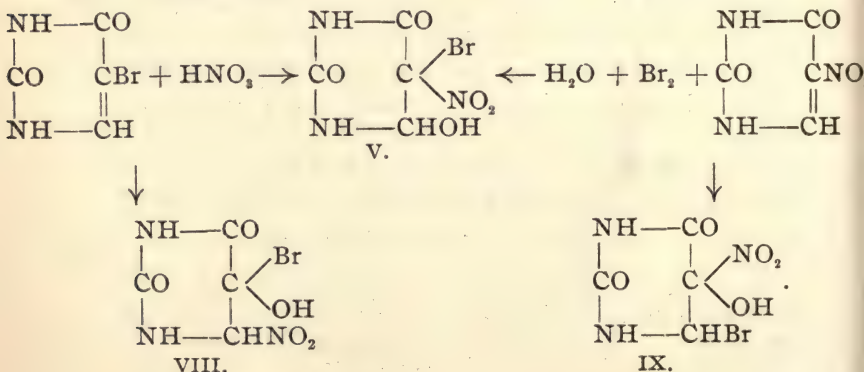
¹ Z. physiol. Chem., **32**, 241.

² Loc. cit.

I now find that the compound II., prepared from 5-bromuracil and nitric acid, is identical with *bromnitrooxyhydrouracil*, V., which Behrend¹ obtained by treatment of nitrouracil with bromine water. This interesting result, and the fact that the analogous compounds, III. and IV., are prepared under the same conditions, indicate that they have a similar structure and are to be considered as oxynitrohydropyrimidines; *viz.*, chlornitrooxyhydrouracil, VI., and oxynitrohydrothymine, VII., respectively:



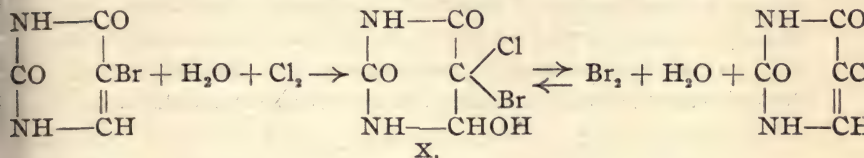
The formation of these hydropyrimidines involves a direct addition of nitric acid to the double bond between the 4 and 5 positions of the pyrimidine ring. The preparation of bromnitrooxyhydrouracil, V., from 5-nitrouracil and 5-bromuracil shows that the nitro group and bromine atom are linked to the same carbon atom. It also proves Behrend's² original conclusion that the formation of oxyhydropyrimidines, from certain pyrimidines, by the action of chlorine and bromine water involves an addition of hypochlorous and hypobromous acids at the double bond.



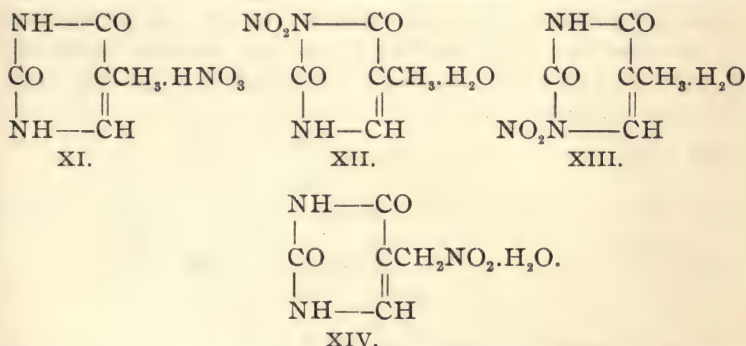
¹ Ann. Chem. (Liebig), **240**, 11.

² Ann. Chem. (Liebig), **229**, 20.

I also find that 5-bromuracil and 5-chloruracil react with chlorine water and bromine water, respectively, giving the same chlorbromoxyhydrouracil, X. When this hydropyrimidine was digested with alcohol it was converted into 5-chloruracil.



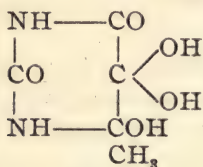
Thymine apparently shows no tendency to form salts with acids. It can be crystallized from concentrated hydriodic and hydrobromic acids without alteration. The possibility of the nitro derivative IV. being a nitric acid salt, XI. is excluded since thymine is not formed by treatment with alkalis, and also because it does not react with bromine water to give oxybromhydrothymine.¹ The compound is not a substituted nitro derivative, as represented by formulas XII., XIII., and XIV., because it does not contain water of crystallization. It can be crystallized repeatedly from absolute alcohol without alteration.



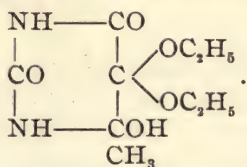
I have made the interesting observation that oxynitrohydrothymine, VII., can exist in two modifications which I have designated by the Greek letters α and β . The two isomers are obtained under practically the same conditions. The α derivative is the stable modification and melts at 183° – 185° . The β derivative melts at 230° – 235° and rearranges to the α form at

¹ Jones: Z. physiol. Chem., 29, 20.

ordinary temperature. The two isomers are especially characterized by their crystalline habit and are converted quantitatively into thymine when reduced with tin and hydrochloric acid. This interesting case of isomerism is possibly similar in nature to that recently observed by Osten.¹ He found, for example, that methylisodialuric acid, XV., and its diethyl ether, XVI., occur in two isomeric modifications which undergo reversible transformations in the presence of acids and alkalis.

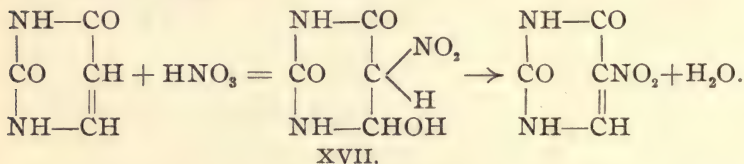


XV.



XVI.

Oxynitrohydropyrimidines are probably formed in every case when 5-nitropyrimidines are obtained by the action of nitric acid. For example: the formation of nitrouracil from uracil probably involves an addition of nitric acid, giving the unstable hydropyrimidine XVII., which then breaks down with loss of a molecule of water, giving nitrouracil. In the case of thymine, on the other hand, the molecule cannot lose water in the normal manner and therefore the intermediate hydropyrimidine, VII., is capable of isolation.

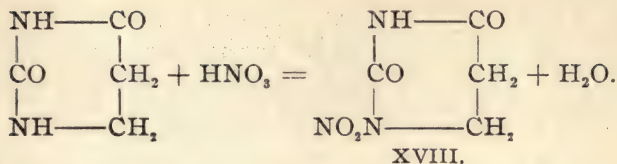


XVII.

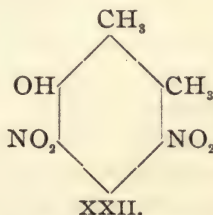
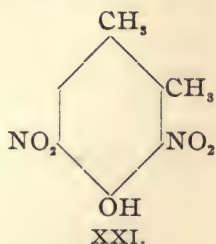
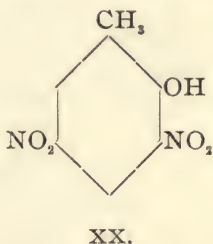
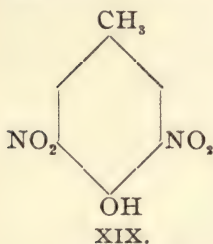
It is interesting to note here the behavior of nitric acid towards hydrouracil.² This compound contains no double bond between the 4 and 5 positions and the 5 position is not the point of attack. It reacts with nitric acid, giving a nitro derivative, XVIII., in which the nitro group is linked to the 3 position of the pyrimidine ring.

¹ Ann. Chem. (Liebig), **343**, 133.

² Franchimont and Friedmann: Rec. trav. chim., **26**, 218.



The isolation of the above oxynitrohydropyrimidines lends new interest to some early observations on the action of nitric acid on certain benzene derivatives. For example: nitric acid reacts with toluene, in presence of sulphuric acid, giving 3, 5-dinitroparacresol, XIX., and 3,5-dinitroorthocresol, XX.¹ Orthoxylene gives a mixture of 3,5-dinitroparaxylenol, XXI., and 3,5-dinitroorthoxylenol,² XXII. Orthocresolsulphonic acid reacts with nitric acid, giving 3,5-dinitroorthocresol,³ XX. Similar observations have also been made in the naphthalene series.⁴ Armstrong explains these abnormal reactions by assuming an addition of nitric acid to a double bond in the benzene ring, giving unstable addition products. These then break down in two ways, either with separation of nitrous acid, giving a phenol, or with loss of water, giving a nitro derivative.



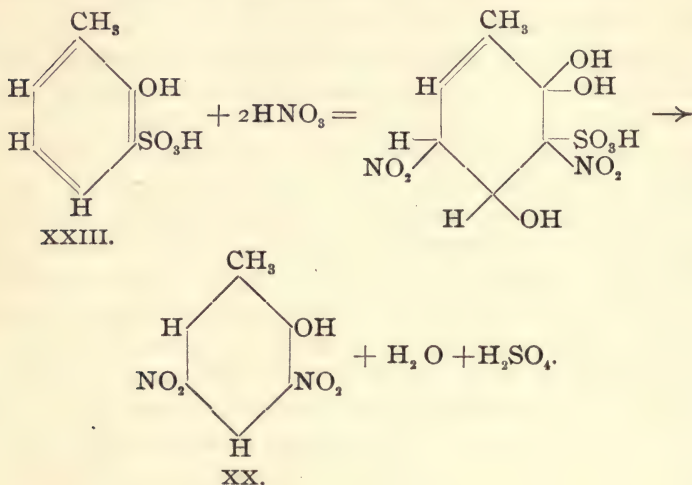
¹ Nolting and Forel: Ber. d. chem. Ges., **18**, 2670.

² Nolting and Pick: *Ibid.*, **21**, 3158.

³ Claus and Jackson: J. prakt. Chem. (2), **38**, 333.

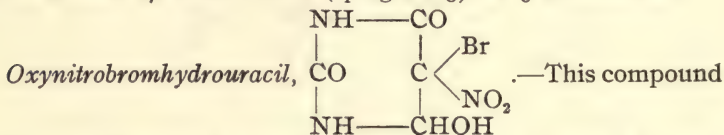
⁴ Armstrong and Rossiter: P. Chem. Soc., **1891**, 87-89; Ber. d. chem. Ges., **24**, R. 721.

The action of nitric acid on orthocresolsulphonic acid, XXIII., may be represented by the following equation. The writer is not aware that such intermediate addition products with nitric acid have been isolated in the benzene series.



EXPERIMENTAL PART.

The Action of Nitric Acid (sp. gr. 1.5) on 5-Bromuracil.



was first described by Behrend.¹ I prepared it in the following manner: Three grams of finely pulverized 5-bromuracil were dissolved in 19 cc. of nitric acid and the solution allowed to evaporate in a vacuum over sulphuric acid. I obtained 3.3 grams of the pure hydropyrimidine which crystallized in large blocks and rectangular prisms. The pyrimidine had no definite melting point, but decomposed from 150° to 165° according to the rate of heating. It was difficultly soluble in cold water but could not be purified by recrystallization from this solvent. When warmed with water above 40° it was decomposed with

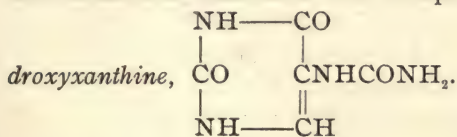
¹ *Loc. cit.*

formation of brompicrin, which was recognized by its disagreeable odor. The pyrimidine did not contain water of crystallization. It agreed in its chemical behavior, so far as I was able to judge, with the hydropyrimidine described by Behrend.

0.3006 gram of substance gave 0.2204 gram CO_2 and 0.0481 gram H_2O . Nitrogen (Kjeldahl).

	Calculated for $\text{C}_4\text{H}_4\text{O}_6\text{N}_3\text{Br}$.	I.	Found.	II.
C	19.00	20.00		...
H	1.57	1.77		...
N	16.53	...		16.35

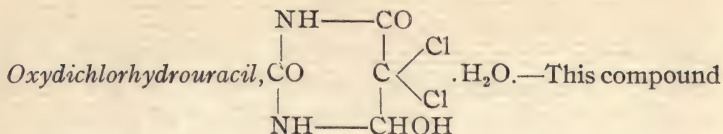
Reduction of Oxynitrobromhydrouracil with Tin and Hydrochloric Acid.—Two grams of the hydropyrimidine were reduced, on the steam bath, for one hour with an excess of tin and hydrochloric acid. The solution was then evaporated to dryness to remove the excess of hydrochloric acid and the residue redissolved in water. The tin was then removed by precipitation with hydrogen sulphide and the filtrate concentrated to a volume of 20 cc. Five grams of potassium cyanate were then added to the solution when I obtained an insoluble, granular precipitate. The compound was difficultly soluble in hot water and practically insoluble in the common organic solvents and dilute sulphuric acid. It did not contain halogens, and left no inorganic residue when burned on a platinum foil. When the compound was warmed with bromine water and then treated with an excess of barium hydroxide solution, a purple precipitate was obtained. Its characteristic properties and nitrogen determinations identified the compound as Behrend's¹ *hy-*



Nitrogen (Kjeldahl):

	Calculated for $\text{C}_5\text{H}_6\text{O}_3\text{N}_4$.	I.	Found.	II.
N	32.94	32.80		32.95

¹ Ann. Chem. (Liebig), **229**, 40; **240**, 6.



was prepared by dissolving uracil in an excess of strong chlorine water, or by oxidizing uracil with potassium chlorate and dilute hydrochloric acid. Five grams of finely pulverized uracil were suspended in about 100 cc. of chlorine water and chlorine gas conducted into the solution until the pyrimidine had dissolved. The excess of chlorine was then removed with a current of air and the solution concentrated on the steam bath. On cooling, prismatic crystals of chloruracil (see below) deposited. These were removed by filtration and the filtrate concentrated further. The hydropyrimidine then separated, on cooling, in the form of tables melting at 205° – 208° with effervescence. In a second experiment 2 grams of uracil were dissolved in 80 cc. of 20 per cent hydrochloric acid and the solution heated to 70° – 90° . Potassium chlorate was then occasionally added in small portions and the oxidation continued at 50° – 60° for four hours. The excess of chlorine was then removed in the usual manner and the solution allowed to stand. The oxydichlorhydrouracil finally separated in stout prisms which decomposed at 208° – 210° . The hydropyrimidine crystallized from water in large, well-developed prisms melting at 212° – 215° with effervescence. Aqueous solutions of the pyrimidine gave a purple precipitate when warmed with a solution of barium hydroxide. The pyrimidine was recovered unaltered after boiling with alcohol for 24 hours. The corresponding dibrom derivative¹ is converted into 5-bromuracil by the same treatment. Oxydichlorhydrouracil contained one molecule of water of crystallization which was determined by heating for one hour at 100° – 110° .

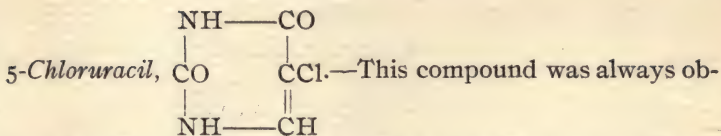
0.9157 gram of substance lost 0.0778 gram of H_2O .

	Calculated for $\text{C}_4\text{H}_4\text{O}_3\text{N}_2\text{Cl}_2 \cdot \text{H}_2\text{O}$.	Found.
H_2O	8.30	8.49

Nitrogen determination for hydrous pyrimidine (Kjeldahl):

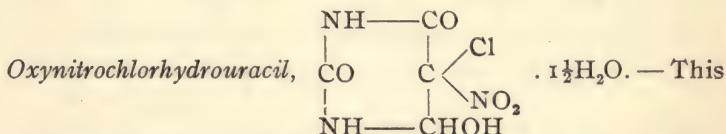
	Calculated for $\text{C}_4\text{H}_4\text{O}_3\text{N}_2\text{Cl}_2 \cdot \text{H}_2\text{O}$.	Found.
N	12.90	12.67

¹ Wheeler and Johnson: J. Biol. Chem., **3**, 183.



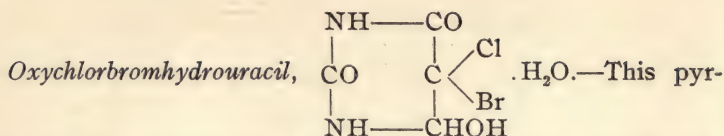
tained associated with oxydichlorhydrouracil when uracil was treated with chlorine water. It can be prepared by reducing the hydropyrimidine with tin and hydrochloric acid. The pyrimidine separated from the acid solution in the form of rectangular prisms and square tables. It was practically insoluble in alcohol and cold water. It crystallized from hot water in prisms melting at 300° – 305° according to the rate of heating. The pyrimidine did not contain water of crystallization. Nitrogen (Kjeldahl):

	Calculated for $\text{C}_4\text{H}_3\text{O}_2\text{N}_2\text{Cl}$.	I.	Found. II.	III.
N	19.11	19.03	19.5	19.00



pyrimidine was prepared by dissolving 1.0 gram of 5-chloruracil in 10 cc. of fuming nitric acid (sp. gr. 1.5). When the solution was allowed to evaporate spontaneously, in the atmosphere, the pyrimidine separated in hard, prismatic crystals. The substance had no definite melting point but decomposed with effervescence from 150° to 160° , according to the rate of heating. It slowly underwent decomposition when heated at 100° – 110° and was also decomposed by boiling water. The compound contained water of crystallization (Analysis I.), which it slowly lost when exposed to the atmosphere. After drying over sulphuric acid, in a desiccator, for 6 days, the analytical determination agreed with the calculated value for the anhydrous material (Analyses II. and III.). (Kjeldahl):

	Calculated for $\text{C}_4\text{H}_4\text{O}_5\text{N}_2\text{Cl} \cdot 1\frac{1}{2}\text{H}_2\text{O}$.	Found. I.	
N	17.75	17.7	
	Calculated for $\text{C}_4\text{H}_4\text{O}_5\text{N}_2\text{Cl}$.	Found. II.	Found. III.
N	20.04	19.57	19.6



imidine can be prepared from 5-bromuracil or 5-chloruracil by dissolving them in an excess of chlorine water and bromine water, respectively. It was very soluble in water and crystallized from bromine water in prismatic crystals, decomposing at $195^\circ\text{--}200^\circ$, with effervescence. It reacted with barium hydroxide, in aqueous solution, giving a purple precipitate. The pyrimidine contained one molecule of water of crystallization, which was determined by heating for one hour at $90^\circ\text{--}110^\circ$. The compound slowly loses its water of crystallization in the atmosphere and becomes anhydrous after standing for several hours in a desiccator over sulphuric acid.

I. 0.7413 gram substance lost 0.0516 gram H_2O .

II. 0.2029 gram substance lost 0.0123 gram H_2O .

	Calculated for $\text{C}_4\text{H}_4\text{O}_3\text{N}_2\text{ClBr} \cdot \text{H}_2\text{O}$.	I.	Found.	II.
H_2O	6.88	6.95		6.50

Nitrogen determination for hydrous pyrimidine (Kjeldahl):

	Calculated for $\text{C}_4\text{H}_4\text{O}_3\text{N}_2\text{ClBr} \cdot \text{H}_2\text{O}$.	Found.
N	10.70	10.66

Nitrogen determination for anhydrous pyrimidine (Kjeldahl):

	Calculated for $\text{C}_4\text{H}_4\text{O}_3\text{N}_2\text{ClBr}$.	I.	Found.	II.
N	11.49	11.31		11.4

Action of Boiling Alcohol on Oxychlorbromhydrouracil.—Five-tenths of a gram of the hydropyrimidine, melting at $195^\circ\text{--}200^\circ$, was dissolved in 20 cc. of absolute alcohol and the solution boiled for ten hours. The alcohol was then removed by evaporation and the product obtained was crystallized from hot water. It separated in stout prisms, decomposing at $300^\circ\text{--}305^\circ$. It gave a test for chlorine and a mix-

ture of the compound and 5-chlorouracil decomposed sharply at 300° – 305° . Analysis (Kjeldahl):

	Calculated for $C_4H_3O_2N_2Cl$.	Calculated for $C_4H_3O_2N_2Br$.	Found.
N	19.11	14.66	19.04

Action of Bromine Water on 5-Iodouracil.—5-Iodouracil was decomposed by bromine water with liberation of iodine. About 1 gram of the pyrimidine was dissolved in bromine water, and the solution allowed to evaporate spontaneously in the atmosphere. Transparent prisms finally separated, which decomposed sharply at 200° – 205° . The compound did not contain iodine, but gave a strong test for bromine. It was converted into 5-bromouracil when heated with absolute alcohol. A nitrogen determination agreed with the calculated value for oxydibromhydrouracil¹ (Kjeldahl):

	Calculated for $C_4H_4O_3N_2Br_2$.	Found.
N	9.72	9.6

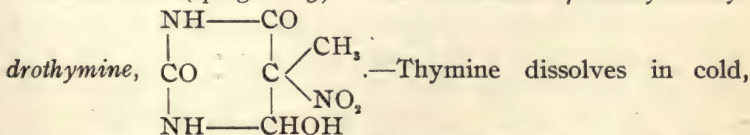
The Action of Nitric Acid on Thymine.

Nitric Acid (sp. gr. 1.415).—Five-tenths of a gram of thymine was dissolved in 2 cc. of concentrated nitric acid and the solution evaporated to dryness on the steam bath. There was no evidence of any reaction and the thymine was recovered unaltered. It deposited from hot water in plates that decomposed at about 321° . When mixed with pure thymine this decomposition point was not lowered.

Analysis (Kjeldahl):

	Calculated for $C_5H_6O_2N_2$.	Found.
N	22.22	22.23

Nitric Acid (sp. gr. 1.5). The Formation of α -Oxynitrohy-



fuming nitric acid with slight evolution of heat. If red fumes are evolved by this treatment it is a safe indication that the

¹ Wheeler and Johnson: *Loc. cit.*

thymine is not pure. The hydropyrimidine was obtained perfectly pure, and the yield was quantitative, when thymine was treated with fuming nitric acid under the following conditions: One gram of thymine was dissolved in 6 cc. of nitric acid and the solution allowed to evaporate at ordinary temperature. The nitro derivative deposited in large, well-developed prisms or blocks, which decrepitated above 130° and melted at 183° with violent effervescence. The compound was soluble in hot water, extremely soluble in alcohol, and separated from both these solvents in blocks that melted at 183° – 185° . It was practically insoluble in benzene. The pyrimidine did not lose weight after heating for 1.5 hours at 100° – 110° and again for one-half hour at 110° – 115° . When heated above 120° it slowly underwent decomposition. The composition of the compound was not altered by recrystallization from absolute alcohol (Analysis III.).

0.2086 gram substance gave 0.2454 gram CO_2 and 0.0695 gram H_2O .

Nitrogen (Kjeldahl):

	Calculated for $\text{C}_6\text{H}_7\text{O}_5\text{N}_3$.	Calculated for $\text{C}_6\text{H}_6\text{O}_2\text{N}_2$.	I.	Found. II.	III.
C	31.74	47.61	32.08	...	...
H	3.70	4.76	3.70	...	...
N	22.22	22.22	...	22.00	21.95

α -Oxynitrohydrothymine dissolves in water, giving an acid reaction. The pyrimidine undergoes decomposition when its aqueous solution is boiled. The addition of barium hydroxide to its aqueous solution produces no precipitate or color; also no thymine deposited when an alcoholic solution of the pyrimidine was treated with ammonia. When the nitropyrimidine was dissolved in concentrated sulphuric acid, and a few drops of ferrous sulphate solution were added, the characteristic test for nitric acid was obtained. α -Oxynitrohydrothymine can also be prepared by dissolving thymine in fuming nitric acid (sp. gr. 1.5) and evaporating the solution to dryness, at once, on the steam bath. This method of nitration can be recommended for preparing quickly small quantities of the hydropyrimidine. The yields are not quan-

titative, since part of the thymine undergoes oxidation. The best results are obtained when 1 gram portions are nitrated under the following conditions: One gram of thymine is dissolved in 4 cc. of nitric acid (sp. gr. 1.5) and the solution evaporated to dryness as quickly as possible. The nitrothymine is obtained as a colorless, crystalline residue which separates from water in blocks decomposing at 183°–185°. It is possible, in this manner, to prepare several grams of the hydropyrimidine in a few minutes. The yields obtained by this method of nitration were very uniform and are given in the table below.

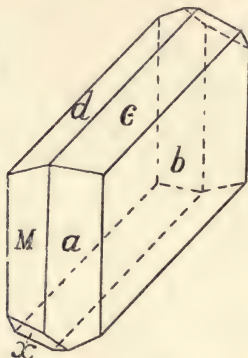
Number.	Nitric acid, sp. gr. 1.5. Cc.	Weight of thymine. Grams.	Weight of crude oxynitrohydrothymine. Grams.	Weight of hydropyrimidine after crystallization from water. M. p. 183°–185°. Grams.	Per cent of theoretical of pure hydrothymine.
1	4	1	1.1	0.80	57.1
2	4	1	1.1	0.82	58.5
3	4	1	1.1	0.79	56.4
4	4	1	1.1	0.81	57.8
5	8	2	2.15	1.60	55.5
6	4	1	1.2	0.90	64.4
7	8	2	2.1	1.50	53.5

Crystallography of Oxynitrohydrothymine.

By W. E. FORD.

The pyrimidine crystallizes in the triclinic system, showing a combination of *b* (010), *c* (001), *a* (100), *M* (110), *d* (034) and *X* (111). The crystals were small, averaging about 2 mm. broad by 1 mm. thick. In habit they present the appearance of diamond-shaped tables with beveled edges, as is illustrated in the figure. The face, *b* (010), is always the most prominent, while the prism with the pinacoid, *a*, and the base with the dome, *d*, form the beveling faces. Frequently one of these latter faces is much subordinated in size, or may be entirely wanting. The negative pyramid, *X*, is always small, and often not present. The crystal faces, although distinct to the eye, were very poorly adapted for measurement with

the reflection goniometer. They were usually quite rough or curved and gave indistinct and broad signals on the goniometer. A series of the crystals was measured on the two-circle goniometer, and the average of the best readings ob-



tained was taken for the fundamental angles, but the angles as given and the crystallographic constants calculated from them can be considered only as proximate. The measured angles were as follows:

$$(010) : (110) = 63^{\circ}54'.$$

$$(010) : (100) = 96^{\circ}15'.$$

$$(010) : (001) = 73^{\circ}38'.$$

$$\text{Zone } (010) : (110) : \text{Zone } (010) : (001) = 79^{\circ}35'.$$

$$\text{Zone } (010) : (110) : \text{Zone } (010) : (101) = 50^{\circ}5'.$$

$$(010) : (034) = 71^{\circ}33'; \text{ calc.} = 71^{\circ}46'.$$

Using the first five measurements as fundamentals, the crystal constants were calculated to be

$$a:b:c = 0.578:1.000:0.420. \quad \alpha = 107^{\circ}35', \beta = 100^{\circ}25', \\ \gamma = 80^{\circ}59'.$$

The crystals show a good cleavage parallel to c (001). On account of the nature of the material only a few of the optical facts concerning the compound could be determined. It possesses a strong double refraction. The extinction direction on b (010) is inclined to the edge between b and a at 31° . The crystals, when looked at in the polariscope in a direction

perpendicular to c (001), the cleavage face, show the emergence of an optic axis nearly in the center of the field.

Action of Nitric Acid (sp. gr. 1.5) in Presence of Concentrated Sulphuric Acid.—There was an immediate reaction, with evolution of red fumes, when 0.5 gram of thymine was dissolved in a mixture of 3 cc. of nitric and 3 cc. of sulphuric acids. When the mixture was allowed to stand, without cooling, the reaction continued to increase in violence, with evolution of heat, and the thymine was completely decomposed. In a second experiment, 1 gram of thymine was dissolved in a cold mixture of 3 cc. nitric and 2 cc. concentrated sulphuric acids. This solution was held at a temperature of 70° – 75° for about three-quarters of an hour, when gas bubbles had practically ceased to be formed. The acid solution was then cooled and poured into 15 cc. of ice water. After standing for several hours, stout, well-developed prisms deposited from the solution. They melted at 183° – 185° , with effervescence, and were identified as *oxynitrohydrothymine*. They were soluble in alcohol and warm water. Analysis (Kjeldahl):

	Calculated for $C_6H_7O_5N_3$.	Found.
N	22.22	21.66

Action of Bromine Water on α -Oxynitrohydrothymine.—One gram of the hydropyrimidine was dissolved in an excess of bromine water and the solution allowed to evaporate spontaneously. There was no evidence of a reaction and oxynitrohydrothymine separated in large, transparent blocks melting at 183° – 185° .

Analysis (Kjeldahl):

	Calculated for $C_6H_7O_5N_3$.	Found.
N	22.22	22.42

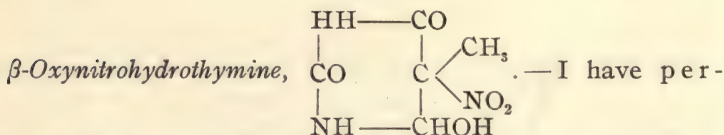
Reduction of α -Oxynitrohydrothymine with Aluminum Amalgam.—Two and five-tenths grams of the hydrothymine were dissolved in cold water and reduced for 1.5 hours with an excess of aluminum amalgam. The temperature was not allowed to rise above 40° during the reduction. After fil-

tering from aluminum amalgam and aluminum hydroxide the filtrate was evaporated to dryness. I obtained a crystalline deposit which was difficultly soluble in cold water, but separated from hot water in plates melting at 320° . When mixed with thymine the melting point was not lowered. It dissolved in fuming nitric acid, giving the original α -oxynitrohydrothymine melting at 183° – 185° . Analysis (Kjeldahl):

	Calculated for $C_6H_6O_2N_2$.	Found.
N	22.22	22.01

Reduction of α -Oxynitrohydrothymine with Tin and Hydrochloric Acid.—Two and two-tenths grams of the hydropyrimidine were reduced for one hour with an excess of tin and concentrated hydrochloric acid. The acid solution was then evaporated to dryness, the residue dissolved in water, and the tin removed by precipitation with hydrogen sulphide. When the aqueous filtrate was concentrated and cooled, thymine separated in glistening plates, decomposing at 320° . Analysis (Kjeldahl):

	Calculated for $C_6H_6O_2N_2$.	Found.
N	22.22	22.10



formed fifteen experiments, during this research, to determine the behavior of fuming nitric acid towards thymine under different conditions. I have taken different amounts of thymine (0.5–5.0 grams), and have varied the proportions of nitric acid. I have also allowed the acid solution to evaporate under different conditions—at room temperature, on the steam oven, in a vacuum over sulphuric acid, and at 100° —but in only two experiments have I observed the formation of β -oxynitrohydrothymine. The conditions under which I obtained this isomer were as follows: One and six-tenths grams of thymine were dissolved in 8 cc. of cold, fuming nitric acid (sp. gr. 1.5) and the solution was allowed to evaporate

in the atmosphere overnight. The following morning large, transparent blocks had deposited, which showed no signs of melting at 183° – 185° , but decomposed at 230° – 235° , according to the rate of heating. One of the crystals selected for analysis weighed 0.2600 gram. The isomer did not revert to the α derivative when crystallized from water or absolute alcohol, but separated, on cooling, in well-developed prisms decomposing at 230° – 236° . In another experiment, 0.5 gram of thymine was dissolved in 10 cc. of fuming nitric acid and the solution allowed to evaporate over sulphuric acid in a vacuum desiccator. I obtained practically a quantitative yield of the β derivative melting at 230° – 235° . The compound did not lose weight when heated for one-half hour at 90° – 100° . Analysis (Kjeldahl):

	Calculated for $C_6H_7O_6N_2$.	I.	Found. II.
N	22.22	22.00	22.1

Reduction of β -Oxynitrohydrothymine with Tin and Hydrochloric Acid.—This compound was reduced in the same manner as the α derivative. The excess of tin was removed with hydrogen sulphide and the filtrate evaporated to dryness. I obtained a crystalline residue which separated from water in plates melting at 315° – 320° . The compound sublimed when heated in a test tube, and when mixed with thymine, the melting point was not lowered. It dissolved in fuming nitric acid, giving α -oxynitrohydrothymine melting at 183° – 185° . Analysis (Kjeldahl):

	Calculated for $C_6H_6O_2N_2$.	Found.
N	22.22	22.31

Rearrangement of β -Oxynitrohydrothymine into α -Oxynitrohydrothymine.—Some of the α -pyrimidine, melting at 183° – 185° , was preserved in a desiccator from May 29, 1907, until January 17, 1908. It apparently underwent no change, and melted at 181° – 183° with effervescence. A sample of the β -pyrimidine, melting at 230° – 235° , was preserved from June 19, 1907, to October 7, 1907. It then decomposed at 227° – 235° , and a nitrogen determination (Kjeldahl) gave 22.00

per cent; calculated, 22.22 per cent nitrogen. This material was not examined again until January 16, 1908. It then had completely rearranged to the α -pyrimidine and melted at 183° – 188° with effervescence. A mixture of this material and pure α -oxynitrohydrothymine melted at 183° – 186° with effervescence. Analysis (Kjeldahl):

	Calculated for $C_6H_7O_5N_3$.	Found.
N	22.22	21.9

I take pleasure in thanking Professor W. E. Ford for the crystallographic description of oxynitrohydrothymine and also Mr. D. B. Jones for his help in this investigation.

NEW HAVEN, CONN.,
Jan. 18, 1908.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES: SYNTHESIS OF URACIL-3-ACETIC ACID.

[THIRTY-FIRST PAPER.]

BY HENRY L. WHEELER AND LEONARD M. LIDDLE.

Received May 8, 1908.

Johnson and Heyl found when methyl iodide and 2-ethylmercapto-6-oxypyrimidine (for nula I) are warmed in alcoholic solution in the presence of potassium hydroxide, that the methyl group substitutes in the 1-position of the pyrimidine and that 1-methyl-2-ethylmercapto-6-oxypyrimidine, II, results.¹ The formation of a 3-methyl derivative has not yet been observed in this reaction. When the mercapto derivative was warmed with hydrochloric acid, 1-methyl uracil, III, was obtained. The structure of this methyl uracil was settled by converting it into 1-methyl-5-nitro-6-oxypyrimidine which had been obtained previously, in a different manner by Behrend and Thurm.²

We have obtained an entirely different result when 2-ethylmercapto-6-oxypyrimidine is treated with ethyl chloracetate and alkali in alcoholic solution. The alkylation in this case, although under similar conditions, takes place in the 3-position and 2-ethylmercapto-6-oxypyrimidine-3-ethyl acetate, IV, is formed.

When this ester is warmed with alkali it dissolves and hydrochloric acid then precipitates 2-ethylmercapto-6-oxypyrimidine-3-acetic acid, V. If this acid is warmed with hydrochloric acid, mercaptan is evolved and uracil-3-acetic acid results, VI.

The mercapto acid, V, was also obtained by heating 2-ethylmercapto-6-oxypyrimidine in alkaline solution with potassium chloracetate and uracil-3-acetic acid can be directly prepared by treating uracil in alkaline solution with chloracetic acid. At this point it seemed possible that alkyl iodides might be found to regularly give 1-alkyl derivatives. We therefore examined the action of ethyliodoacetate on uracil and it was found that this gave the same acid as the chlorine compound.

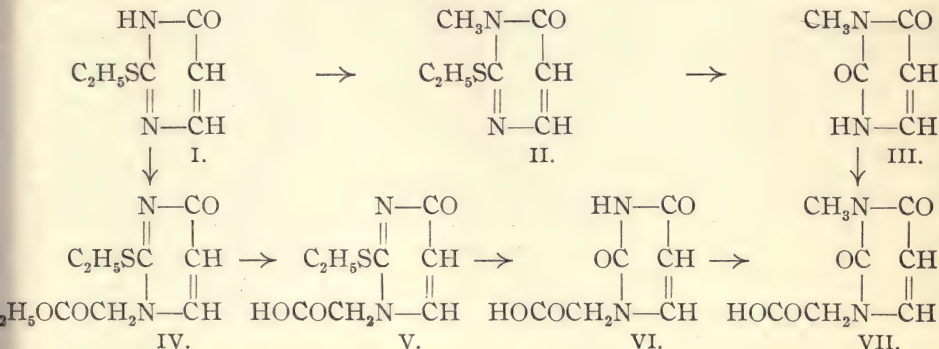
It is evident from these results that the structure of each new alkyl derivative must be determined separately and uracil-3-acetic acid should be of service in this direction.³ The proof of the structure of the acetic acid compounds was obtained as follows: Johnson and Heyl's 1-methyl-uracil, III, was treated with chloracetic acid and an excess of alkali;

¹ THIS JOURNAL, 37, 628 (1907).

² Ann. (Liebig), 323, 160.

³ The above results also show that alkylation does not give any clue to the position of hydrogen in the substance alkylated. Since 2-ethylmercapto-6-oxypyrimidine is soluble in alkali it is represented as having the NH-CO group with hydrogen in the 1-position.

this gave 1-methyluracil-3-acetic acid, VII, and the same methyl acid was formed when our uracil acetic acid, VI, was methylated with methyl iodide and potassium hydroxide in methyl alcohol. The structure of these compounds and their relations are expressed in the following formulas:



Experimental Part.

2-Ethylmercapto-6-oxypyrimidine-3-ethyl Acetate (formula IV, above). Molecular proportions of sodium, 2-ethylmercapto-6-oxypyrimidine and ethylchloracetate were dissolved in alcohol, in the order named, and the mixture was warmed until it no longer gave an alkaline reaction (2-3 hours). The solution, filtered from sodium chloride, gave a thick oil on evaporating to dryness. When this was shaken with ether and water it deposited prismatic crystals. The material was crystallized from water; 5 grams dissolved in about 20 cc. of hot water and on cooling bunches of beautiful, long, colorless prisms separated which melted to a clear oil, without effervescence, at 129° . Analysis:

Calculated for $\text{C}_{10}\text{H}_{14}\text{O}_3\text{N}_2\text{S}$; N_2 11.57; found, 11.87.

This ester is readily soluble in alcohol and in dilute alkali.

2-Ethylmercapto-6-oxypyrimidine-3-acetic Acid (formula V).—The solution of the above ester in dilute alkali gave no precipitate when acidified with acetic acid. On adding hydrochloric acid in slight excess a granular precipitate was formed. This was found to be very soluble in hot alcohol and moderately so in cold. It is difficultly soluble in water. The long, slender prisms from alcohol had a fern-like growth and melted at $208-209^\circ$ with some effervescence.

Calculated for $\text{C}_8\text{H}_{10}\text{O}_3\text{N}_2\text{S}$; N, 13.08; found, 13.12.

Five grams of 2-ethylmercapto-6-oxypyrimidine were dissolved in two molecular proportions (3.6 grams) of potassium hydroxide and three grams of chloracetic acid in 5 cc. of water were added. When this solution was evaporated nearly to dryness on the steam bath, 1.5 grams of unaltered 2-ethylmercapto-6-oxypyrimidine separated. The solution

was filtered, made alkaline with sodium hydroxide and reheated a short time on the steam bath. On cooling and adding hydrochloric acid 3.1 grams of the above mercapto acid were obtained. When this material was warmed with strong hydrochloric acid, on the steam bath, mercaptan was evolved and uracil-3-acetic acid was obtained.

Uracil-3-acetic Acid (formula VI).—The above mercapto acid and ester are quantitatively converted into uracil-3-acetic acid by means of hydrochloric acid. It was found, however, that uracil-3-acetic acid could be more conveniently prepared directly from uracil as follows: An aqueous solution of uracil (10.2 grams) in two molecular proportions of potassium hydroxide was boiled with the calculated quantity of chloracetic acid. When the solution gave an acid reaction it was made alkaline by the addition of a few drops of potassium hydroxide. When it finally remained alkaline after 10 minutes boiling, it was cooled and acidified with hydrochloric acid. The yield of uracil-3-acetic acid (10.8 grams) was 70 per cent. of the theoretical. The acid was readily soluble in hot water and moderately soluble in cold. It formed small blocks or tables which melted with effervescence at 285° . It was nearly insoluble in methyl or ethyl alcohol.

Calculated for $C_6H_6O_4N_2$: N, 16.47; found, 16.57, 16.69.

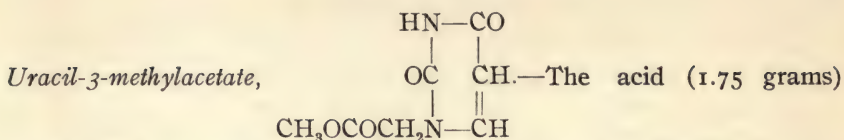
This acid showed no tendency to form a hydantoin. It was found to be very stable when heated with acids. It was obtained unaltered when boiled for 10 hours with hydrochloric acid. It dissolved in boiling acetic anhydride and on evaporating and crystallizing the residue from 85 per cent. alcohol, or water, unaltered acid was obtained. It was also obtained unaltered when heated with 20 per cent. sulphuric acid for one and a half hours at 200° . It gave no color with bromine water and barium hydroxide.

The *potassium salt* of uracil-3-acetic acid, prepared by dissolving the acid in the calculated quantity of potassium hydroxide, crystallized in long, flat prisms which were very soluble in cold water.

The *copper salt* was obtained as a minutely crystalline light blue salt on mixing a solution of the potassium salt with one of copper sulphate. Silver and zinc sulphates also gave crystalline salts while the precipitates obtained with mercuric chloride and lead acetate were amorphous.

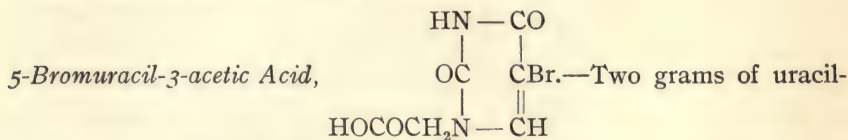
The *barium salt* obtained by dissolving the acid in a solution of barium hydroxide and then removing the excess of barium by carbon dioxide and concentrating, formed balls of needles like uracil. It was readily soluble in hot water. It was not decomposed by acetic acid.

Calculated for $(C_6H_5O_4N_2)_2Ba$: N, 11.77; found, 11.46.



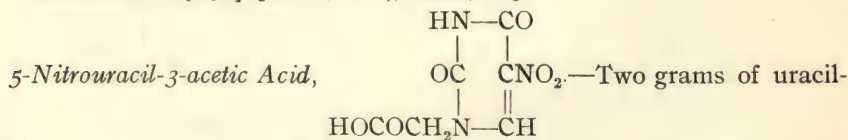
was esterified in methyl alcohol (50 cc.) with a few drops of concentrated sulphuric acid. On evaporating to about 15 cc. and cooling, 1.2 grams or 63 per cent. of the ester separated. It was readily soluble in hot water and hot alcohol. It formed beautiful colorless needles and although it was repeatedly crystallized from water it melted as if it was a mixture, partially melting at about 177° , then melting to a clear oil at about 216° . Its appearance and the following nitrogen determination indicated that it was pure.

Calculated for $\text{C}_7\text{H}_8\text{O}_4\text{N}_2$: N, 15.29; found, 15.13.



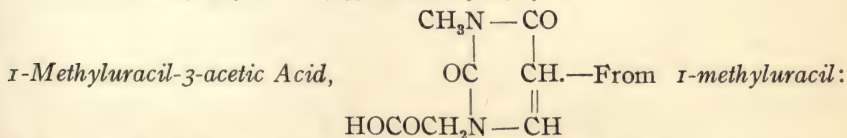
3-acetic acid dissolved in water were treated with an excess of bromine and the solution was then allowed to evaporate in the air. On drying the residue over sulphuric acid, it weighed 2.8 grams or 96 per cent. of the calculated yield for a monobrom substitution product. It was readily soluble in hot water, difficultly so in cold and nearly insoluble in alcohol. It formed bunches of colorless needles which melted with effervescence at 244° .

Calculated for $\text{C}_6\text{H}_5\text{O}_4\text{N}_2\text{Br}$: N, 11.24; found, 11.58.



3-acetic acid were treated with 10 cc. of concentrated nitric acid and 5 cc. of concentrated sulphuric acid on the steam bath. In twenty minutes a crop of colorless crystals had separated, weighing 1.75 grams or 70 per cent. of the calculated amount. This material was readily soluble in hot water and difficultly soluble in alcohol. It formed colorless prisms which melted with effervescence at $264-265^\circ$.

Calculated for $\text{C}_6\text{H}_5\text{O}_6\text{N}_3$: N, 19.55; found, 19.66, 19.28.



A mixture of 2.6 grams methyl uracil, 3 grams of chloracetic acid

and 3.2 grams of potassium hydroxide in 20 cc. of water were warmed on the steam bath. In a half hour the solution was acid to litmus. It was made alkaline and boiled for a short time. On acidifying the solution with hydrochloric acid and cooling, crystals separated; this material weighed 2.7 grams. It crystallized from water in needle-like prisms or in prismatic plates, and melted constantly at 239° – 240° to a clear oil without effervescence. It forms beautiful, transparent prisms from alcohol.

Analysis I.

From Uracil-3-acetic Acid: Uracil acetic acid (1.2 grams) and four molecular proportions of potassium hydroxide were dissolved in a little water. An excess of methyl iodide (5 grams) was added and sufficient methyl alcohol to effect solution. The mixture was allowed to stand in a warm place for two days when the solution was acid to litmus. It was evaporated to dryness and the residue was crystallized from water containing a little sulphur dioxide. This gave 0.6 gram of material crystallizing in thin prismatic plates and having properties identical with the acid from 1-methyl uracil. When these substances were mixed, the melting point was not lowered. Analysis II.

Calculated for $C_7H_8O_4N_2$: N, 15.21; found: I, 15.18; II, 15.41.

NEW HAVEN, CONN., May, 1908.

[Reprinted from the Journal of the American Chemical Society. Vol. XXX.
No. 7. July, 1908.]

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES: SYNTHESIS OF URACIL-4-ACETIC ACID.

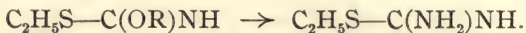
[THIRTY-SECOND PAPER.]

BY HENRY L. WHEELER AND LEONARD M. LIDDLE.

Received May 8, 1908.

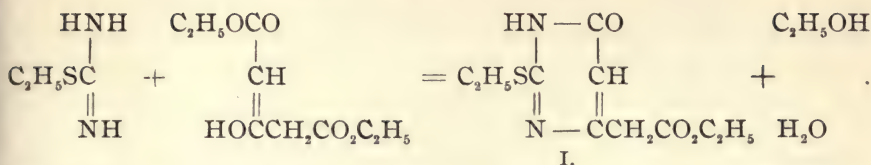
Pinner has shown that acetone dicarboxylic ester condenses with benzamidine giving phenyloxypyrimidine acetic ester.¹ He also found that the ester condenses with other aromatic amidines of the general formula, $R-C(NH_2)NH$. Acetamidine and phenylacetamidine, he states did not give crystalline products.

The pseudothiureas may be viewed as amidines derived from the iminothiocarbonic esters. 2-Ethylpseudothiurea is ethylthiocarbamidine or mercaptoformamidine:

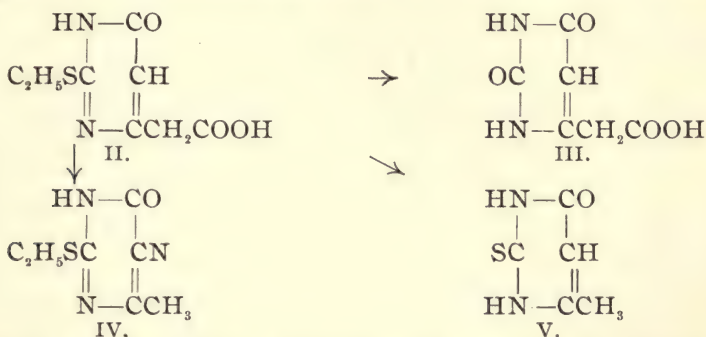


In accordance with this we have found that 2-ethylpseudothiurea condenses very smoothly, in alkaline solution, with acetonedietiethylcarboxylate, yielding 2-ethylmercapto-6-oxypyrimidine-4-ethyl acetate (I). The condensation may be represented as follows:

¹ *Ber.*, 28, 480 (1895).



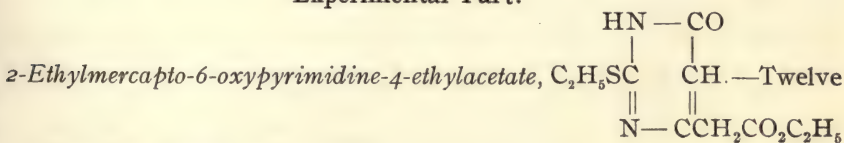
When this pyrimidine ester, I, is warmed with aqueous alkali it is readily saponified, and on acidifying the solution with hydrochloric acid, 2-ethylmercapto-6-oxypyrimidine-4-acetic acid, II, is obtained. When this mercapto acid is digested on the steam bath with concentrated hydrochloric acid, mercaptan is given off and uracil-4-acetic acid, III, results.



On melting 2-ethylmercapto-6-oxypyrimidine-4-acetic acid, carbon dioxide escapes and the material is converted into 2-ethylmercapto-4-methyl-6-oxypyrimidine, IV. If melted in a stream of dry hydrogen chloride ethyl chloride is given off, in addition to carbon dioxide, and 2-thio-4-methyluracil, V, is formed. These last two pyrimidines have been described by List¹ who obtained them in a different manner.

The action of dry hydrogen chloride on the mercaptopyrimidines, leading to the formation of 2-thiopyrimidines with loss of alkyl halide, is a new reaction in the pyrimidine series. We have found that it can be applied in other cases. Taken in connection with the action of dilute nitric acid (Marckwald²) or hydrogen peroxide (Traube³) we are now able to replace a 2-alkylmercapto group by hydrogen. This is of importance for synthetic work since formamidine has not yet been shown to lend itself to pyrimidine condensations.

Experimental Part.



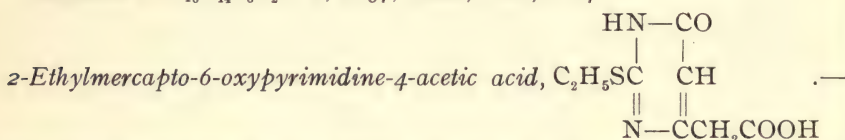
¹ *Ann. chem. (Liebig)*, **236**, 3 (1886).

² *Ber.*, **25**, 3112 (1892).

³ *Ann. chem. (Liebig)*, **331**, 71 (1904).

grams of potassium hydroxide were dissolved in 20 cc. of water and to this cold solution 18.3 grams of the ethyl bromide addition product of thiourea were added. As soon as solution took place, 20 grams of acetone diethylcarboxylate were slowly added and the mixture was allowed to stand for about an hour, then warmed for a short time on the steam bath. On cooling, and acidifying with acetic acid, 17 grams of the condensation product separated. This was found to be very soluble in hot alcohol, hot water and acetic acid, less soluble in cold alcohol and nearly insoluble in cold water. On crystallizing from hot alcohol long, colorless, silky needles were obtained which melted sharply to an oil at 131° .

Calculated for $C_{10}H_{14}O_3N_2S$: N, 11.57; found, 11.60, 11.67.



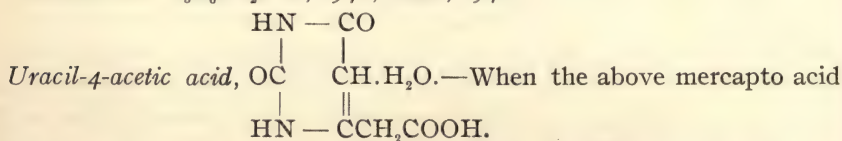
Two grams of the above ester were dissolved in 25 cc. of water containing 1.5 grams of potassium hydroxide. The solution was heated on the steam bath for a half hour, then cooled and the acid precipitated with hydrochloric acid. The crystalline precipitate weighed 1.5 grams or 86 per cent. of the calculated. It was readily soluble in hot alcohol and it gave burrs of colorless needles. It was less soluble in water and it melted at 155° with vigorous effervescence.

Calculated for $C_8H_{10}O_3N_2S$: N, 13.08; found, 13.10, 13.24.

This acid is not precipitated from alkaline solution by acetic acid.

One gram of 2-ethylmercapto-6-oxypyrimidine-4-acetic acid was heated in an oil bath at 170° until effervescence ceased. The residue was decolorized with charcoal and recrystallized from water. It melted at $145-147^{\circ}$, and when mixed with 2-ethylmercapto-4-methyl-6-oxypyrimidine the melting point was not altered. One gram of the acid was melted in an oil bath at 170° and a stream of dry hydrogen chloride was then allowed to pass over the substance. It immediately solidified. On crystallizing from water, it formed colorless prisms which gave a strong test for sulphur. This material had all the properties of 2-thio-4-methyluracil. Analysis:

Calculated for $C_5H_6ON_2S$: N, 19.71; found, 19.78.



was warmed on the steam bath with concentrated hydrochloric acid, it readily evolved mercaptan and gave a quantitative yield of uracil-

4-acetic acid. The acid was crystallized from water. It formed flat prisms which sintered above 300° and melted with effervescence at 340° . In concentrated aqueous solution, it separates at first in an anhydrous condition then in crystals containing one molecule of water.

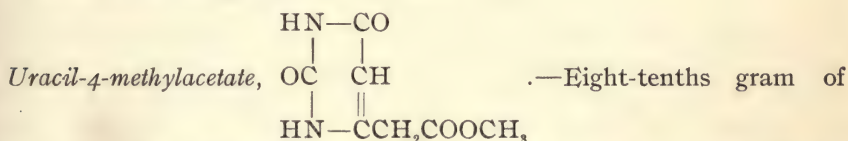
Calculated for $C_6H_6O_4N_2 \cdot H_2O$: $H_2O = 9.57$; found, 9.97.

Calculated for $C_6H_6O_4N_2$: N, 16.47; found, 16.95.

Uracil-4-acetic acid is soluble in about 8 parts of boiling water and in 30 parts of cold. It is much less soluble in alcohol. It is a strong acid and the aqueous solution reddens litmus. It does not give a precipitate with barium chloride or mercuric chloride. It forms an amorphous silver salt soluble in ammonia.

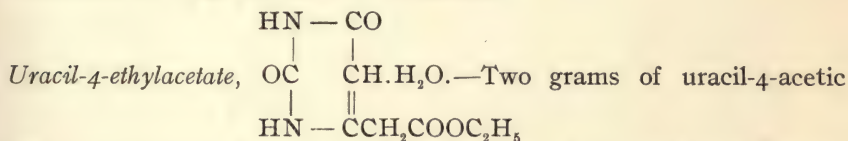
The Potassium Salt, $C_6H_5O_4N_2K$.—Two grams of the acid were dissolved in a little water containing 0.7 gram of potassium hydroxide. On adding alcohol, balls of a minute, colorless crystal separated. The salt was very soluble in water and insoluble in alcohol. It was dried in a desiccator for analysis.

Calculated for $C_6H_5O_4N_2K$: N, 13.46; found, 13.40.



anhydrous acid was esterified by dissolving in 15 cc. of methyl alcohol containing two drops of concentrated sulphuric acid and warming the solution for one hour. On concentrating the solution to about 7 cc., 0.5 gram of ester separated. The material was washed with water and recrystallized from water. It then formed large, elongated, six-sided prisms which melted to an oil at $216-218^{\circ}$ with slight effervescence. It was very soluble in hot water and hot alcohol. It was dried over sulphuric acid for analysis.

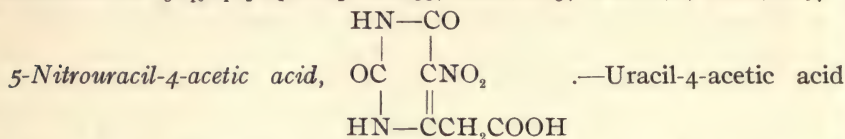
Calculated for $C_7H_8O_4N_2$: N, 15.21; found, 15.39.



acid were dissolved in 25 cc. of absolute alcohol containing several drops of concentrated hydrochloric acid and the solution was boiled for three hours. It was then evaporated to dryness and the residue crystallized three times from about 90 per cent. alcohol. There was then obtained about 0.8 gram of ester. It was very soluble in hot alcohol and it separated, on cooling, in colorless prisms, which curiously contained a molecule of water of crystallization. This is the first pyrimidine ester

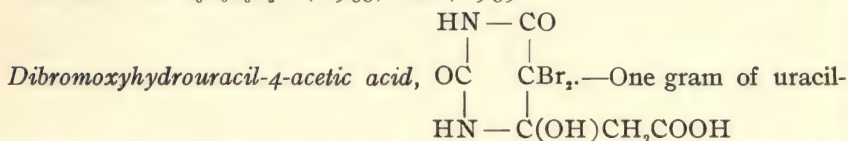
that has been found to have water of crystallization. It melted to an oil at 187–189°. It was dried over sulphuric acid for analysis.

Calculated for $C_8H_{10}O_4N_2 \cdot H_2O$: $H_2O = 8.33$; found, 8.25; $N = 12.96$; found, 12.97.



was nitrated by dissolving 1 gram of the acid in 4 cc. of a mixture of two parts concentrated nitric acid and one of sulphuric acid. The solution was then heated on the steam bath. The product was insoluble in alcohol and difficultly soluble in hot water. It formed minute cubes which melted with effervescence at 153°.

Calculated for $C_6H_5O_6N_3$: $N, 19.53$; found, 19.39.



4-acetic acid was dissolved in water and a large excess of bromine was added. On spontaneous evaporation colorless, elongated plates separated. They became dark colored above 180° and melted with effervescence at 240°. The substance appears to crystallize with a half molecule of water of crystallization.

Calculated for $C_6H_5O_5N_2Br_{2.1} \cdot \frac{1}{2}H_2O$: $H_2O = 2.54$; found, 2.89. $N = 7.87$, found, 7.55.

A nitrogen determination in the case of the substance dried at 106° gave 8.43 per cent. nitrogen while the calculated is 8.10 per cent.

NEW HAVEN, CONN., May, 1908.

IX. RESEARCHES ON PYRIMIDINS: SYNTHESSES OF SOME NITROGEN-ALKYL DERIVATIVES OF CYTOSIN, THYMIN AND URACIL.

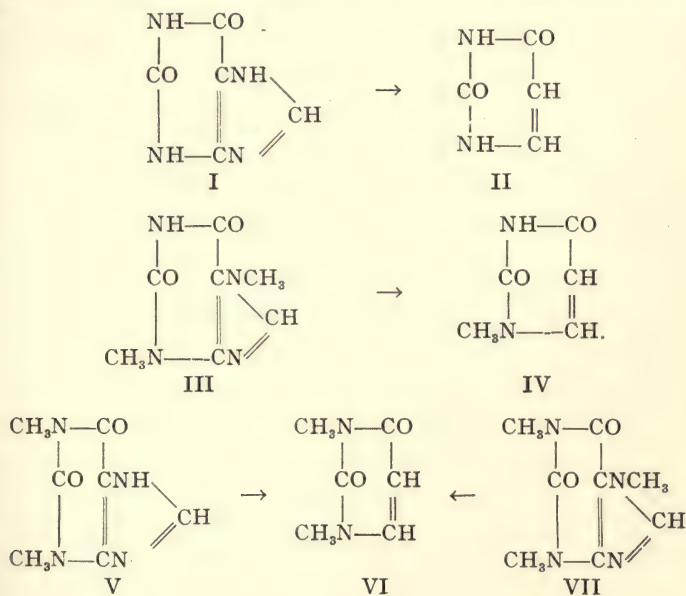
(Thirty-third Paper.)

BY TREAT B. JOHNSON AND SAMUEL H. CLAPP.

(From the Sheffield Laboratory of Yale University.)

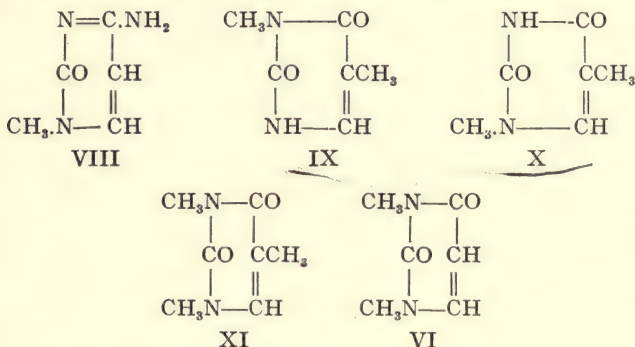
(Received for publication, May 28, 1908.)

The nitrogen-methyl derivatives of cytosin, thymin and uracil are of especial interest because of the occurrence of methyl-purins in nature. Purins may be considered as compound rings in which imidazol has been grafted into pyrimidins. A similar relationship exists between 3-methyluracil, IV, 1,3-dimethyl-uracil, VI, and the purins, theobromin, III, theophyllin, V, and caffen, VII, as exists between uracil, II, and xanthin, I.



These alkyl derivatives are also of interest because of the possibility that future investigations may show the presence of methylpyrimidins in animal or vegetable organisms. It is interesting to note here that Suzuki, Aso and Mitarai,¹ in a paper titled "Ueber die chemische Zusammensetzung der japanischen Sojasauce oder Schoyu," have described a decomposition product of *Schoyu* to which they have assigned the empirical formula $C_9H_9N_3$. They state that the compound is probably an isomer of *aminodimethyl pyrimidin*.²

We shall describe in this paper the syntheses and properties of 3-methylcytosin, VIII, 1-methylthymine, IX, 3-methylthymine, X, 1,3-dimethylthymine, XI, and 1,3-dimethyluracil, VI.



Two nitrogen-methyl derivatives of thymine and uracil have been described in the literature, viz: 1,3-dimethylthymine, XI, and 1-methyluracil, XII. Dimethylthymine³ was prepared by heating the mono-potassium salt of thymine with methyl iodide at 150°. We prepared this compound and also 1,3-dimethyluracil, VI, by warming thymine and uracil respectively in alcoholic solution with the required proportions of potassium hydroxide and methyl iodide.

1-Methyluracil, XII, was described in a paper from this laboratory⁴ and was prepared in the following manner:

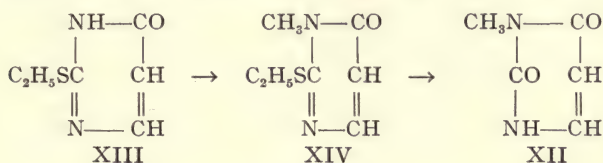
¹ C. Blatt: ii, 1649, 1907. *Bull. College Agr.*, Tokio, vii, 477.

² Schwarze: *Journ. f. prakt. Chem.*, xlii, p. 1; Schlenker: *Ber. d. deutsch. chem. Gesellsch.*, xxxiv, p. 2819; Schmidt: *ibid.*, xxxv, p. 1577.

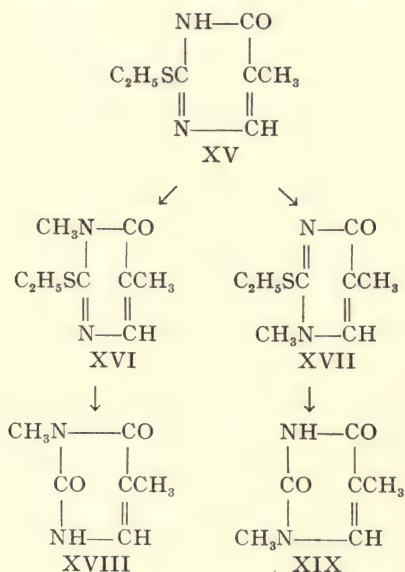
³ Steudel: *Zeitschr. physiol. Chem.*, xxx, p. 539.

⁴ Johnson and Heyl: *Amer. Chem. Journ.*, xxxvii, p. 628.

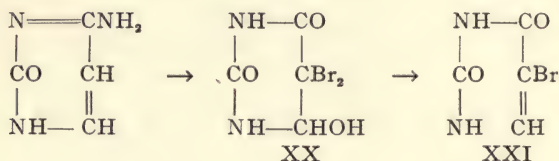
1-methyl-2-pseudoethylthiourea was condensed with the sodium salt of ethyl formylacetate giving 1-methyl-2-ethylmercapto-6-oxypyrimidin, XIV. This same mercaptopyrimidin was also obtained by treatment of 2-ethylmercapto-6-oxypyrimidin, XIII, with methyl iodide in presence of alkali. Hydrolysis of this mercaptopyrimidin with hydrochloric acid gave 1-methyluracil, XII.



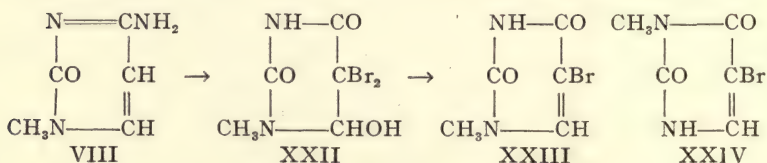
We now find that 2-ethylmercapto-5-methyl-6-oxypyrimidin XV, reacts with methyl iodide in presence of potassium hydroxide giving about equal proportions of the two isomeric pyrimidins—1,5-dimethyl-2-ethylmercapto-6-oxypyrimidin, XVI (m. 65°) and 3,5-dimethyl-2-ethylmercapto-6-oxypyrimidin, XVII (m. 156°). Hydrolysis of these mercaptopyrimidins with concentrated hydrochloric acid gave 1-methylthymine, XVIII (m. 202° to 205°) and 3-methylthymine, XIX (m. 280° to 282°), respectively.



The structures of the isomeric methylthymins and incidentally the corresponding mercaptopyrimidins were established in the following manner: Wheeler and Johnson¹ have shown that cytosin reacts smoothly with bromine water giving oxydibromhydrouracil, XX. When this hydropyrimidin was digested with alcohol it was converted quantitatively into 5-bromuracil, XXI. Since the 6-amino radical is removed by this treatment,



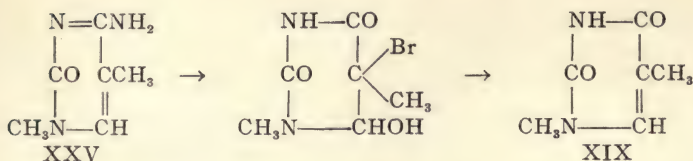
it seemed probable to the writers that substituted cytosin derivatives would behave in a similar manner giving substituted uracils. Our experimental data confirms this assumption. We find that cytosin reacts with methyl iodide in presence of potassium hydroxide giving 3-methylcytosin, VIII. This pyrimidin reacted with bromine water giving a quantitative yield of 3-methyloxydibromhydrouracil, XXII. When this hydropyrimidin was warmed with alcohol it was converted into 3-methyl-5-bromuracil, XXIII, melting at 255° to 260°. The isomeric 1-methyl-5-bromuracil² XXIV, melts at 228° to 229°. 5-Methylcytosin apparently reacts with methyl iodide in a similar manner as cytosin giving 3,5-dimethylcytosin, XXV. When this



pyrimidin was treated successively with bromine water and alcohol, it was converted quantitatively into 3-methylthymine, XIX, melting at 280° to 282°. This result also proves that the

¹ This *Journal*, iii, p. 183.

² Johnson and Heyl: *Loc. cit.*



mercaptopyrimidin, XVII, which melts at 156° , is a 3-methyl derivative since it gives 3-methylthymine on hydrolysis.

The introduction of methyl groups into uracil, thymine, and cytosine, has a similar influence on their physical properties as in the case of purins. They increase the solubility and lower the melting points. For example: while uracil and thymine are difficultly soluble in alcohol, the methyl derivatives of these pyrimidins dissolve easily in this solvent and are moderately soluble in cold water. The 3-methyl derivatives of 2-ethylmercapto-5-methyl-6-oxypyrimidin, thymine and 5-bromouracil are more soluble in water than the isomeric 1-methylpyrimidins.

It is also interesting to note that the 3-methylpyrimidins melted higher, in every series examined, than the isomeric 1-methylpyrimidins:

2-Ethylmercapto-1,5-dimethyl-
6-oxypyrimidin.
(65°)

2-Ethylmercapto-3,5-dimethyl-
6-oxypyrimidin.
(156°)

1-Methylthymine.
(202° to 205°)

3-Methylthymine.
(280° to 282°)

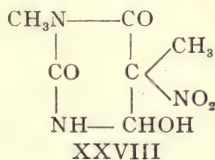
1-Methyloxynitrohydrothymine.
(135° to 136°)

3-Methyloxynitrohydrothymine.
(178° to 181°)

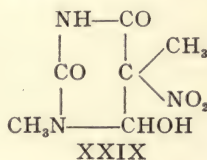
1-Methyl-5-bromouracil.
(228° to 229°)

3-Methyl-5-bromouracil.
(255° to 260°)

1-Methylthymine and 3-methylthymine reacted in a similar manner with fuming nitric acid as thymine giving characteristic oxynitrohydrothymins,¹ XXVIII and XXIX.

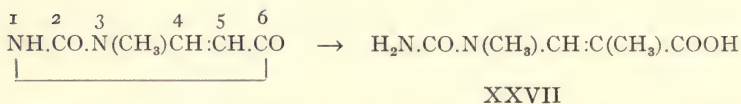
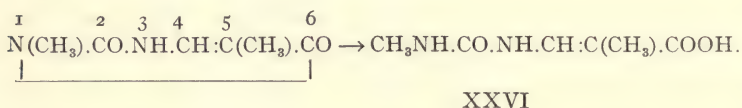


and



¹ Johnson: *Amer. Chem. Journ.*, xl; *This Journal*, iv, p. 407.

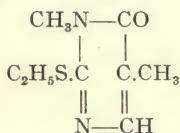
Conductivity measurements on thymine and its methyl derivatives disclosed the interesting facts that thymine and 1,3-dimethylthymine gave practically constant conductivities at 25°. On the other hand, 1-methylthymine and 3-methylthymine gave abnormal conductivities which increased with the length of time these pyrimidines were kept in solution (see Appendix). This interesting behavior is possibly due to a slow hydrolysis of the pyrimidine ring giving, in solution, β -uraminoacrylic acids, XXVI and XXVII.



The methyl derivatives of thymine, described in this paper, should be of interest to the pharmacologist. It is a well known fact that the methylated dioxypurins possess a pronounced diuretic action. Sweet and Levene¹ have recently shown that the administration of thymine to a dog also caused a most pronounced diuresis. Whether the methylated thymine will possess a higher diuretic action than thymine must be decided by further study.

EXPERIMENTAL PART.

2-Ethylmercapto-1,5-dimethyl-6-oxypyrimidin:



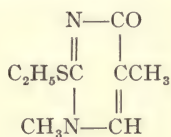
Five grams of 2-ethylmercapto-5-methyl-6-oxypyrimidine and a molecular proportion of potassium hydroxide (1.6 grams) were dissolved in boiling 95 per cent alcohol. An excess of

¹ *Journ. of Exper. Med.*, ix, p. 229.

methyliodide was then added and the solution boiled for about one hour when it no longer reacted alkaline to turmeric. The undissolved potassium iodide was filtered off and the filtrate heated on the steam-bath to remove the excess of alcohol. We obtained an oily residue, which deposited a mixture of 2-ethylmercapto-1,5-dimethyl-6-oxypyrimidin and unaltered 2-ethylmercapto-5-methyl-6-oxypyrimidin, when triturated with cold water. The filtrate contained the isomeric 2-ethylmercapto-3,5-dimethyl-6-oxypyrimidin (see below). 2-Ethylmercapto-1,5-dimethyl-6-oxypyrimidin was freed from the unaltered material by treatment with a small volume of a cold, dilute solution of sodium hydroxide. The weight of the crude pyrimidin was 2.1 grams or 30 per cent of the theoretical. It was purified for analysis by crystallization from hot water, and separated, on slow cooling, in long, slender prisms which melted at 65° to a clear oil without effervescence. It did not contain water of crystallization. It was dried for analysis over sulphuric acid (Kjeldahl):

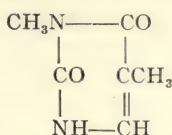
	Calculated for $C_8H_{12}ON_2S$:	Found:
N.....	15.22	15.17

2-Ethylmercapto-3,5-dimethyl-6-oxypyrimidin:



In order to isolate this pyrimidin from the above filtrate, the solution was evaporated to dryness and the residue extracted several times with cold chloroform. When the chloroform was evaporated, at ordinary temperature, 1.8 gram of the crude pyrimidin were obtained, or 33.4 per cent of the theoretical. The compound crystallized from benzene in prisms which melted at 156° to a clear oil without effervescence. It was dried for analysis over sulphuric acid (Kjeldahl):

	Calculated for $C_8H_{12}ON_2S$:	Found:
N.....	15.22	15.20

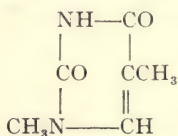
1,5-Dimethyl-2,6-dioxypyrimidin (1-methylthymin):

A quantitative yield of this pyrimidin was obtained when 2-ethylmercapto-1,5-dimethyl-6-oxypyrimidin was digested with hydrobromic acid until the evolution of ethylmercaptan ceased (8 hours). The acid solution was then evaporated to dryness and the pyrimidin crystallized from water. It separated in aggregates of stout prisms which melted at 202° to 205° , with effervescence, to a clear oil. The compound was readily soluble in boiling alcohol and acetone. It did not contain water of crystallization. Analysis:

0.2680 gram of substance gave 0.5081 gram of CO_2 and 0.1379 gram H_2O .

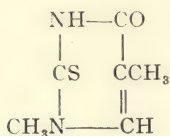
Nitrogen determination (Kjeldahl):

	Calculated for $\text{C}_6\text{H}_8\text{O}_2\text{N}_2$:	I.	Found: II.	III.
C.....	51.43	51.71		
H.....	5.71	5.71		
N.....	20.00		20.07	20.07

3,5-Dimethyl-2,6-dioxypyrimidin (3-methylthymin):

This pyrimidin was not the only product formed when 2-ethylmercapto-3,5-dimethyl-6-oxypyrimidin was digested with hydrobromic acid for 5 hours. When the acid solution was evaporated to dryness, we obtained a mixture of 3-methylthymin and a compound which was difficultly soluble in cold water. The latter was soluble in warm alcohol and crystallized from hot water in needles melting at 229° to 230° , without effervescence to a clear oil. It was soluble in alkalis and gave a strong test for sulphur. The analytical determinations indi-

cated that the compound was *2-thio-3,5-dimethyl-6-oxypyrimidin*. Analysis (Kjeldahl):

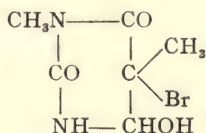


	Calculated for $\text{C}_6\text{H}_8\text{ON}_2\text{S}$:	Found:
		I. II.
N.....	17.95	18.4 18.3

3-Methylthymin is more soluble in cold water than this 2-thiopyrimidin and separated, nearly pure, when the aqueous filtrates (above) were concentrated and cooled. It was purified for analysis by recrystallization from water and melted, when heated slowly, at 280° to 282° to a clear oil. This pyrimidin showed a very characteristic behavior when crystallized from hot water. When the hot, saturated, aqueous solution was quickly cooled, the pyrimidin separated immediately as a bulky, homogeneous mass of long, prismatic needles. On standing, these prisms soon disintegrated, apparently redissolved, and were replaced by characteristic octahedral prisms. The transformation was complete in a few minutes. The compound did not contain water of crystallization. Analysis (Kjeldahl):

	Calculated for $\text{C}_6\text{H}_8\text{O}_2\text{N}_2$:	Found:
N.....	20.00	19.91

1-Methyl-5-brom-4-oxhydrothymin:

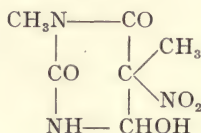


This compound was obtained when 1-methylthymin was dissolved in an excess of bromine water and the solution allowed to evaporate in a vacuum over sulphuric acid. It crystallized from bromine water in stout prisms and melted, on slow heating,

at about 123° to 125° to a clear oil. It was dried for analysis over sulphuric acid (Kjeldahl):

	Calculated for $C_6H_9O_3N_2Br$:	Found:
N.....	11.81	11.92

1-Methyl-5-nitro-4-oxyhydrothymine:

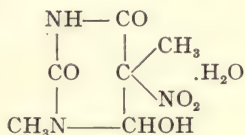


This compound was prepared by dissolving 1-methylthymine in a small volume of fuming nitric acid (sp. gr. 1.5) and allowing the solution to evaporate spontaneously in the air. It deposited in well-developed prisms melting at about 135° to 136° with effervescence. Analysis:

- I. 0.0844 gram substance gave 15.5 cc. moist N_2 at 21° and 728 mm.
 II. Nitrogen determination (Kjeldahl):

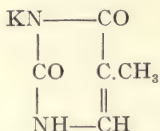
	Calculated for $C_6H_9O_5N_3$:	Found:	
		I.	II.
N.....	20.69	20.84	21.1

3-Methyl-5-nitro-4-oxyhydrothymine:



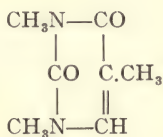
This pyrimidine was prepared in the same manner as its isomer. It separated in large prisms which decomposed at about 178° to 181° with effervescence. This decomposition point varies according to the rate of heating. A nitrogen determination indicated that the compound contained one molecule of water of crystallization. It slowly underwent decomposition when heated at 100° . Analysis (Kjeldahl):

	Calculated for $C_6H_9O_5N_3 \cdot H_2O$:	Calculated for $C_6H_9O_5N_3$:	Found:
N.....	19.00	20.69	18.74

Mono-potassium salt of thymin:

Finely pulverized thymin and a molecular proportion of potassium hydroxide were dissolved in boiling absolute alcohol and the solution boiled for four hours. The potassium salt separated, on cooling, in long needles. It was purified for analysis by recrystallization from 95 per cent alcohol. Nitrogen determinations in the salt, dried to a constant weight at 110°, agreed with the calculated value in a mono-potassium salt of the closed ring (Kjeldahl):

	Calculated for $\text{C}_5\text{H}_5\text{O}_2\text{N}_2\text{K}$:	Found:	
		I.	II.
N.....	17.07	17.22	17.32

1, 3-Dimethylthymin:

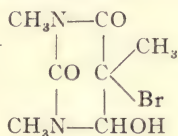
This pyrimidin was first described by Steudel.¹ We obtained the same derivative, in a smooth manner, under the following conditions: Five grams of thymin and 4.6 grams of potassium hydroxide were dissolved in 90 cc. of 95 per cent alcohol and an excess of methyl iodide added to the warm solution. The solution was boiled for twenty minutes, then evaporated to dryness, and the crystalline residue extracted several times with cold chloroform. When the chloroform was evaporated we obtained 2.7 grams of the dimethyl pyrimidin. It was very soluble in water and chloroform and difficultly soluble in ether and petroleum ether. It crystallized from alcohol in

¹ *Loc. cit.*

long needles melting sharply at 153° to a clear oil. Analysis (Kjeldahl):

	Calculated for $C_7H_{10}O_2N_2$:	Found:
N	18.18	18.32

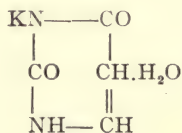
1,3-Dimethyl-5-brom-4-oxyhydrothymin:



Was prepared by dissolving 1, 3-dimethylthymin in bromine water. When the aqueous solution was concentrated in a vacuum, the pyrimidin separated in prisms melting at 132° to 133° to a clear oil. Analysis (Kjeldahl):

	Calculated for $C_7H_{11}O_3N_2\text{Br}$:	Found:
N	11.16	11.25

Mono-potassium salt of uracil:



One molecular proportion of potassium hydroxide was dissolved in 450 cc. of absolute alcohol and 13 grams of finely pulverized uracil suspended in the solution. After digesting for eight hours the uracil was completely changed into the potassium salt. It was difficultly soluble in absolute alcohol and very soluble in cold water. It separated from dilute alcohol in balls of long needles. The yield was quantitative. The salt contained one molecule of water of crystallization which was determined by heating at 120° .

I.	0.3365 gram substance lost	0.0351 gram H_2O .
II.	0.2871 " " "	0.0302 " "

	Calculated for $C_4H_3O_2N_2K.H_2O$:	Found:
		I. II.
H_2O	10.70	10.43 10.52

Nitrogen determination in salt dried at 160° (Kjeldahl):

	Calculated for $C_4H_3O_2N_2K$:	Found:	
		I.	II.
N.....	18.67	18.51	18.55

Potassium determination in the hydrous salt:

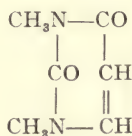
0.1727 gram substance gave 0.0775 gram KCl.

	Calculated for $C_4H_3O_2N_2K \cdot H_2O$:	Calculated for $C_4H_3O_2N_2K$:	Found:
K.....	23.21	25.98	23.55

Nitrogen determination in hydrous salt (Kjeldahl):

	Calculated for $C_4H_3O_2N_2K \cdot H_2O$:	Calculated for $C_4H_3O_2N_2K$:	Found:
N.....	16.67	18.65	16.81

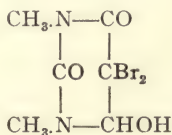
1,3-Dimethyluracil:



This compound was prepared by warming, in alcoholic solution, molecular proportions of potassium hydroxide and the potassium salt of uracil with an excess of methyl iodide. After boiling for three hours the solution was evaporated to dryness and the pyrimidin extracted with chloroform. It crystallized from a mixture of alcohol and ether in long, slender prisms which melted at 121° to 122°. It was extremely soluble in cold water, alcohol and chloroform, but insoluble in ether and petroleum ether. Nitrogen (Kjeldahl):

	Calculated for $C_6H_8O_2N_2$:	I.	Found:	
			II.	III.
N.....	20.00	20.05	20.06	20.24

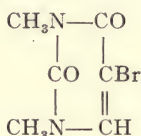
1,3-Dimethyl-dibromoxyhydrouracil:



This pyrimidin crystallized from bromine water in microscopic prisms with curved outline. It melted at 135° to 136° to a clear oil. Analysis (Kjeldahl):

	Calculated for $C_6H_8O_3N_2Br_2$:	Found:
N.....	8.86	9.0

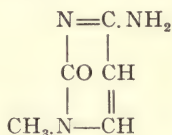
1, 3-Dimethyl-5-bromuracil:



This compound was prepared by digesting the above hydro-uracil derivative with absolute alcohol. It was purified for analysis by recrystallization from water and melted at 181° to 182° to a clear oil. Analysis (Kjeldahl):

	Calculated for $C_6H_7O_2N_2Br$:	Found:
N.....	12.79	13.0

2-Oxy-3-methyl-6-aminopyrimidin (3-methylcytosin):



Six and eight-tenths grams of anhydrous cytosin and 3.4 grams of potassium hydroxide were dissolved in 60 cc. of boiling, absolute alcohol, and 16 grams of methyl iodide added to the solution. After boiling for two hours the solution was evaporated to dryness and the residue of pyrimidin and potassium iodide dissolved in cold water. The iodine was removed with silver sulphate and the excess of silver by precipitation with hydrogen sulphide. The sulphuric acid was then quantitatively removed with barium hydroxide and the filtrate from barium sulphate concentrated to a small volume. The base was precipitated from this solution with a hot, saturated solution of mercuric chloride and the mercury precipitate decomposed in

the usual way with hydrogen sulphide; the chlorine removed with silver sulphate, the excess of silver with hydrogen sulphide, and the sulphuric acid with barium hydroxide. When this solution was evaporated to dryness we obtained about 1.1 gram of the pyrimidin associated with a small amount of unaltered cytosin. The small yield is partly explained by the fact that the base volatilizes with aqueous vapors. It was purified by recrystallization from methylalcohol. It separated in beautiful, distinct prisms which decomposed at about 278° to 279° to a dark oil. This decomposition point varies according to the rate of heating. The base was extremely soluble in water and did not contain water of crystallization. Analysis (Kjeldahl):

	Calculated for $C_5H_7ON_3$:	Found:	
		I.	II.
N.....	33.60	33.57	33.9

The chloroplatinate of 3-methylcytosin:

Was prepared by adding a solution of platinum chloride to a hydrochloric acid solution of the base. It crystallized from water in long, slender prisms. The salt contained two molecules of water of crystallization which was determined by heating at 120° .

I. 0.0513 gram salt lost	0.0028 gram H_2O .
II. 0.2103 " " "	0.0111 " "
III. 0.0841 " " "	0.0045 " "

	Calculated for $(C_5H_7ON_3.HCl)_2.PtCl_4.2H_2O$:	Found:		
		I.	II.	III.
H_2O	5.18	5.45	5.28	5.35

Platinum determination in anhydrous salt:

I. 0.0478 gram salt gave	0.0142 gram Pt.
II. 0.1991 " " "	0.0591 " "
III. 0.0793 " " "	0.232 " "

	Calculated for $(C_5H_7ON_3.HCl)_2.PtCl_4$:	Found:		
		I.	II.	III.
Pt.....	29.54	29.71	29.68	29.26

Picrate of 3-methylcytosin:

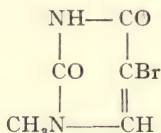
This salt was very insoluble in cold water, and crystallized from hot water in long prisms. The decomposition point varies

greatly according to the rate of heating. When heated slowly it decomposed at about 280° with effervescence. Analysis:

0.1351 gram substance gave 28.7 cc. N_2 at 25° and 770 mm.

	Calculated for $C_5H_7ON_3 \cdot C_6H_5O_7N_3$	Found:
N.....	23.73	24.0

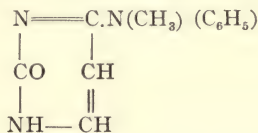
3-Methyl-5-bromuracil:



When 3-methylcytosin was dissolved in a little cold water and liquid bromine added to the solution, a heavy precipitate was obtained. This dissolved immediately, on warming, and after heating about ten minutes on the steambath, the solution was evaporated to dryness under diminished pressure. The residue obtained was then dissolved in a small amount of absolute alcohol and the solution boiled for five hours. On cooling, the brompyrimidin separated in needles. It crystallized from hot water in long, slender, distorted needles. They decomposed at about 255° to 260° to a clear oil with practically no effervescence. The compound was soluble in cold, dilute sodium hydroxide solution and was precipitated again by acetic acid. It gave a strong test for bromine. A mixture of the pyrimidin and the isomeric 1-methyl-5-bromuracil¹ melted at 175° to 195° . A mixture of the pyrimidin and 5-bromuracil melted from 230° to 270° . It did not contain water of crystallization. Analysis (Kjeldahl):

	Calculated for $C_5H_5O_2N_2Br$:	Found:
		I. II.
N.....	13.66	13.53 13.68

2-Oxy-6-methylphenylaminopyrimidin:

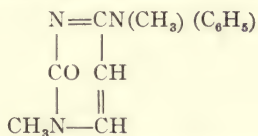


¹ Johnson and Heyl: *Loc. cit.*

Ten grams of 2-ethylmercapto-6-chlorpyrimidin and two molecular proportions of monomethylaniline (twelve grams) were dissolved in dry benzene and the solution boiled for eight hours. The benzene was then evaporated, the residue dissolved in ammonia and the excess of monomethylaniline removed by distillation with steam. When this solution was concentrated we obtained the mercaptopyrimidin as an oil which did not solidify on standing. The crude mercapto derivative was converted into the oxygen derivative by digesting with hydrobromic acid. The yield was 80 per cent of the theoretical. The compound is very insoluble in water and chloroform and crystallizes from alcohol in beautiful hexagonal tables which do not decompose below 285°. Analysis (Kjeldahl):

	Calculated for $C_{11}H_{11}ON_3$:	Found:
N.....	20.90	20.71

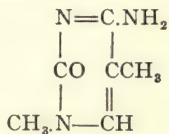
2-Oxy-3-methyl-6-methylphenylaminopyrimidin:



Seven and five-tenths grams of 2-oxy-6-methylphenylaminopyrimidin, 2.1 grams of potassium hydroxide, and 12 grams of methyl iodide were dissolved in 150 cc. of absolute alcohol and the solution boiled for two hours. The solution was then evaporated to dryness and the residue extracted with chloroform. When the chloroform was evaporated we obtained the hydriodide of the pyrimidin base. The base was obtained by decomposing the salt with sodium hydroxide and weighed 5.5 grams or 69 per cent of theoretical. It crystallized from water in long, striated prisms which melted sharply at 186° to 187° to a clear oil without effervescence. Analysis (Kjeldahl):

	Calculated for $C_{12}H_{13}ON_3$:	Found:
N.....	19.53	19.78

2-Oxy-3,5-dimethyl-6-aminopyrimidin (3,5-Dimethyl-cytosin):

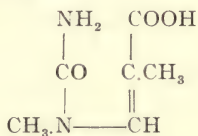


5-Methylcytosin¹ was converted into this base by alkylation with potassium hydroxide and methyl iodide in the usual manner, and the new pyrimidin isolated in the same way as 3-methylcytosin. The compound was extremely soluble in water and volatilized with aqueous vapors. It separated from methylalcohol in prisms. It had no definite melting point, but decomposed from 300° to 310°, according to the rate of heating, with effervescence. Analysis (Kjeldahl):

	Calculated for C ₈ H ₉ ON ₃ :	Found;	
		I.	II.
N.....	30.22	30.09	29.76

Conversion of 3,5-dimethylcytosin into 3-methylthymin:

Some 3,5-dimethylcytosin was dissolved in strong bromine water, the solution warmed on the steambath for ten minutes, and then evaporated to dryness in a vacuum. We obtained a crystalline deposit which was digested with absolute alcohol for five hours. The alcohol was then removed by evaporation and the residue redissolved in hot water. Needle-like prisms separated, on cooling, which melted at 160° with effervescence to a colorless oil. This oil immediately solidified on cooling and then melted at 280° to 282° to an oil without effervescence. They did not contain bromine and were soluble in alkalies. We did not obtain enough of this material for analysis but it was probably *β-methyluramino-α-methylacrylic acid*:



When the filtrate (above) was concentrated and cooled the characteristic crystals of 3-methylthymin separated. They melted at 280° to 282° to an oil. A mixture of pure 3-methylthymin and this compound melted at the same temperature. Analysis (Kjeldahl):

	Calculated for C ₈ H ₉ O ₂ N ₂ :	Found;
		I.
N.....	20.00	20.3

¹ Wheeler and Johnson: *Amer. Chem. Journ.*, xxxi, p. 591.

CONDUCTIVITY MEASUREMENTS ON THYMIN, 1-METHYLTHYMIN, 3-METHYLTHYMIN, 1,3-DIMETHYLTHYMIN AND 4-METHYLURACIL.

BY N. A. MARTIN.

In a series of conductivity measurements on thymin and its nitrogen-methyl derivatives it was found that the conductivities of thymin and 1,3-dimethylthymin remained nearly constant. The very slight increase in conductivity observed was probably due to small amounts of impurities absorbed from the glass and air. The conductivity of water was found to increase at about the same rate.

On the other hand, duplicate determinations on 1-methylthymin and 3-methylthymin did not give agreeing results nor could dissociation constants be calculated. The investigation showed that the conductivity of these two pyrimidins rose with the length of time they were kept in solution. The greatest rise in conductivity was observed in the determinations on 3-methylthymin.

The measurements were carried out by the customary Kohlrausch method in a thermostat at 25°. The water used was redistilled over barium hydroxide, rejecting all that gave a test for ammonia with Nessler's reagent, until it had a specific conductivity of approximately 2×10^{-6} , and the conductivity vessel, pipettes, etc., were thoroughly steamed before using.

The rise in conductivity was determined by preparing 20 cc. of exactly $\frac{N}{64}$ solution of the substance directly in the vessel and measuring its conductivity, at intervals, until it remained practically constant. The rise in specific conductivity of pure water, due to absorption of air, solution of soda from the walls of the vessel, etc., was also determined and found to be practically zero (0.072 per hour).

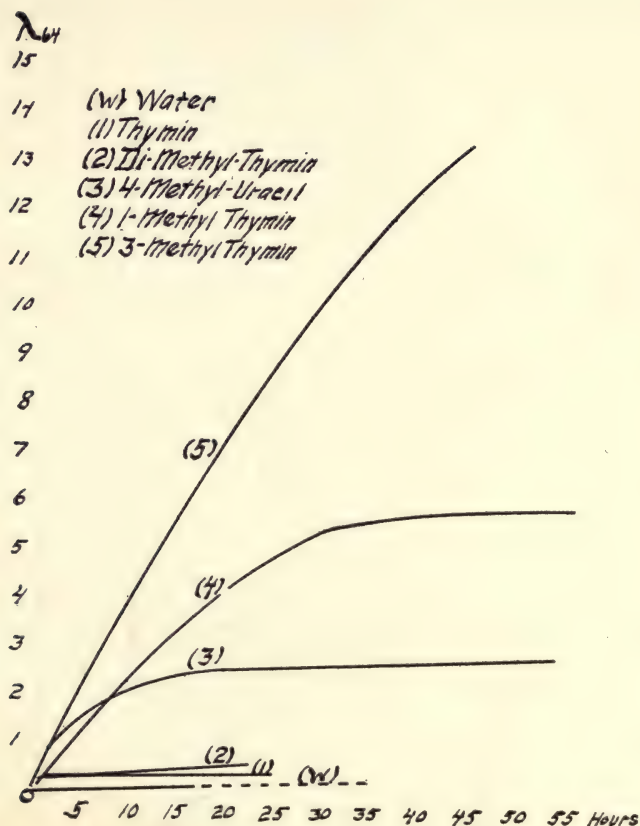
In calculating results the amount of hydrolysis could not be determined as the amount of dissociation of the resulting uraminoacrylic acids (?) was unknown. The specific and molecular conductivities were calculated and the latter plotted as ordinates with the time in hours as abscissas. As a reference line the rise in conductivity of water was also plotted, using 64,000 times the specific conductivity to agree with the molecular conductivity of the solutions ($\lambda_{64} = 64,000 x$).

Molecular conductivity of the pyrimidins in $\frac{N}{64}$ solution at 25°, showing increase due to hydrolysis.

Time.	Thymin.	1,3-Dimethyl- thymin.	1-Methylthymin.	3-Methyl- thymin.	4-Methyl- uracil.
$\frac{1}{3}$ hour		0.23			0.35
$\frac{5}{6}$ "					0.75
1 "		0.37	0.49	0.38	
2 "	(+ $\frac{1}{2}$) 0.41		(+ $\frac{1}{2}$) 1.04	0.90	
3 "	0.42		1.17		
4 "	0.44		1.36		
5 "	0.45		1.54		
6 "	0.46				
7 "	0.47		1.98		
8 "					
17 "		0.68			2.50
18 "		0.69			2.53
19 $\frac{1}{2}$ "		0.72			2.67
20 "		0.74			
22 "		(+ $\frac{1}{2}$) 0.75	4.51		
23 "	(+ $\frac{1}{2}$) 0.57		4.67		
24 "	0.57		4.96	8.90	
25 "					
26 "					
27 "			5.28	10.19	
28 "			5.56		
30 "			5.75		
41 "				13.53	
49 $\frac{2}{3}$ "					2.97
55 $\frac{1}{2}$ "			6.02		

Specific conductivity of $\frac{N}{64}$ pyrimidin solutions at 25°, showing increase due to hydrolysis.

Time.	H ₂ O.	Thymin.	1,3-Di-methyl-thymin.	1-Methyl-thymin.	3-Methyl-thymin.	4-Methyl-uracil.
$\frac{1}{3}$ hour	0.0 ₅ 21		0.0 ₅ 36			0.0 ₅ 55
$\frac{5}{6}$ "						0.0 ₄ 12
1 "	0.0 ₅ 22		0.0 ₅ 57	0.0 ₅ 77	0.0 ₅ 60	
2 "	0.0 ₅ 24	(+ $\frac{1}{2}$) 0.0 ₅ 65		(+ $\frac{1}{2}$) 0.0 ₄ 162	0.0 ₄ 14	
3 "	0.0 ₅ 26	0.0 ₅ 66		0.0 ₄ 182		
4 "		0.0 ₅ 67		0.0 ₄ 212		
5 "		0.0 ₅ 69		0.0 ₄ 240		
6 "		0.0 ₅ 71				
7 "		0.0 ₅ 72 +		(+ $\frac{1}{2}$) 0.0 ₄ 308		
8 "		0.0 ₅ 74				
17 "	0.0 ₅ 55		0.0 ₄ 107			0.0 ₄ 39
18 "			0.0 ₄ 109			0.0 ₄ 40
19 $\frac{1}{2}$ "						0.0 ₄ 42
20 "			0.0 ₄ 113			
22 "			0.0 ₄ 115	0.0 ₄ 704		
23 "		(+ $\frac{1}{2}$) 0.0 ₅ 89	0.0 ₄ 116	0.0 ₄ 730		
24 "				0.0 ₄ 775	0.0 ₅ 139	
25 "						
26 "		0.0 ₅ 91				
27 "		0.0 ₅ 92		0.0 ₄ 824	0.0 ₅ 159	
28 "		0.0 ₅ 93		0.0 ₄ 868		
30 "				0.0 ₄ 898		
41 "					0.0 ₅ 211	
49 $\frac{3}{4}$ "						0.0 ₄ 47
55 $\frac{1}{2}$ "				0.0 ₄ 991		



X. RESEARCHES ON PYRIMIDINS: THE ACTION OF DIAZOBENZENE SULFONIC ACID ON THYMIN, URACIL AND CYTOSIN.

(Thirty-fourth Paper.)

BY TREAT B. JOHNSON AND SAMUEL H. CLAPP.

(From the Sheffield Laboratory of Yale University.)

(Received for publication, June 9, 1908.)

We have, at the present time, practically no knowledge of the way in which the pyrimidins—thymin, uracil and cytosin—are linked in the nucleic acid molecule. The question whether they are actually as such contained in the nucleic acids, from which they are obtained, has not been settled. The recent work of Osborne and Heyl¹ on triticonucleic acid, and of Levene and Mandel² would seem to indicate that they do not result from the purin bases,³ but that the pyrimidin nucleus is present in nucleic acids in the simple form.

In order to obtain new data, which might prove of service in settling the question of the nature of the linking of pyrimidins in nucleic acids, we undertook this investigation. We shall describe the behavior of diazobenzene sulfonic acid on thymin, uracil, cytosin and some of their alkyl derivatives.⁴ A summary of the results of our experiments, and their significance, is given at the end of this paper.

Burian⁵ has investigated the action of diazobenzene sulfonic acid on several nucleic acids and purins. He examined the nucleic acids from sperma, thymus, yeast and spermatozoa of the

¹ *Amer. Journ. of Physiol.*, xxi, p. 157.

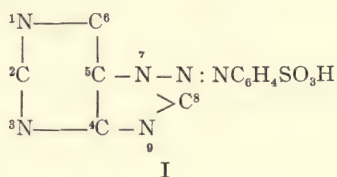
² *Biochem. Zeitschr.*, ix, p. 233.

³ Asher-Spiro: *Ergeb. d. Physiol.*, v, p. 795, 1905; Burian: *Zeitschr. f. physiol. Chem.*, li, p. 438, 1907.

⁴ Johnson and Clapp: *This Journal*, v, p. 49.

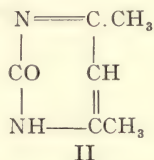
⁵ *Ber. d. deutsch. chem. Gesellsch.*, xxxvii, p. 708; *Zeitschr. f. physiol. Chem.*, li, p. 435.

herring; and states that they do not react with this reagent. He showed, on the other hand, that the purins—xanthin, hypoxanthin, guanin, adenin and theophyllin—in which the hydrogen in position 7 is unsubstituted, react with diazobenzene sulfonic acid, in presence of alkali, giving intensely colored compounds. He regards the compounds formed as diazoamino derivatives of the general formula I. Substitution in the pyrimidin (alloxan)



ring apparently had no influence on the reaction. On the other hand, he observed that purins substituted in position 7—theobromin, caffein—and also uric acid, do not react with the diazo acid. Burian concludes from these results that the xanthin bases are linked in the nucleic acids at the nitrogen atom in position 7.

So far as the writers are aware Evans¹ was the first investigator to observe that a diazobenzene derivative reacts with a pyrimidin giving a colored compound. He found, for example, that 2-oxy-4,6-dimethylpyrimidin, II,



combines with diazobenzene chloride, in presence of alkali, giving a red compound. He says: "Es ist dies ein sehr kräftiger Farbstoff." The compound was unstable and no formula was assigned it.

Steudel² afterwards observed that natural thymin reacts with diazobenzene sulfonic acid, in alkaline solutions, giving an intense

¹ *Journ. f. prakt. Chem.*, xlviii, p. 489.

² *Zeitschr. f. physiol. Chem.*, xlii, p. 170.

red color. Pauly also mentions this diazo reaction in a later publication¹ and states that it cannot be used to distinguish between the pyrimidin and imidazol rings. He observed, for example, that 4-methyluracil gives as intense a color with diazobenzene sulfonic acid as histidin.

We now find that not only thymin and 4-methyluracil, but also uracil, 4,5-dimethyluracil, cytosin, 5-methylcytosin and 5-bromuracil react under proper conditions with diazobenzene sulfonic acid giving red colored solutions. The colors obtained with thymin, 4-methyluracil, 4,5-dimethyluracil and 5-methylcytosin are much more intense than those obtained with uracil, cytosin and 5-bromuracil. Apparently, the character of the groups occupying the 4 and 5 positions has a decided influence on the intensity of the color.

We have also made the interesting observation that the formation of red colors is entirely inhibited by substitution in the 3 positions of the uracil, cytosin and thymin molecules. The assumption that the diazo compound might react at the 4 position of the pyrimidin ring² giving azo derivatives is excluded by Pauly's observation³ and also by the fact that 4, 5-dimethyluracil reacts with the diazo acid giving a red color. Substitution in position 1 of thymin does not prevent the formation of a red color. 1-Methylthymin,⁴ for example, gave as intense a color as thymin itself. On the other hand a red color was not obtained with the diazo acid when the hydrogens in positions 1 and 3 or 3 alone of thymin were substituted by methyl groups.

Similar observations were also made in the cases of uracil and 5-bromuracil. While these pyrimidins gave red colors with the diazo acid, no colors were obtained when 1,3-dimethyluracil⁵ and 3-methyl-5-bromuracil were tested with the reagent. The corresponding 3-methyluracil is unknown. The formation of a color in the cases of cytosin, III, and 5-methylcytosin, VI, is not dependent upon the presence of the free amino radical. 2-Oxy-

¹ *Zeitschr. f. physiol. Chem.*, xlii, p. 512.

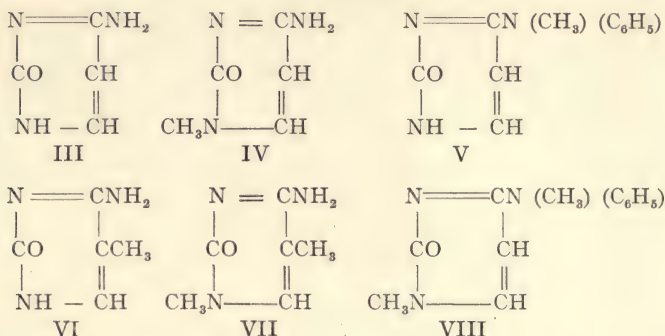
² Burian: *Zeitschr. f. physiol. Chem.*, xlii, p. 297; Mann's *Chemistry of the Proteids*, p. 431, 1906.

³ *Loc. cit.*

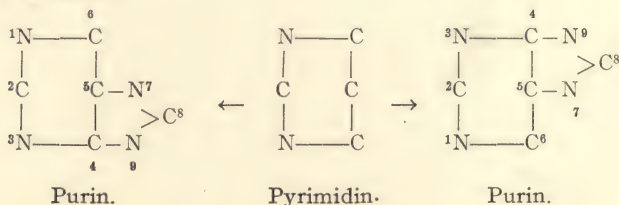
⁴ Johnson and Clapp: *Loc. cit.*

⁵ *Ibid.*

6-methylphenylaminopyrimidin V,¹ gave as intense a color as cytosin, III, while, on the other hand, no color was obtained with 3-methylcytosin, IV, 3,5-dimethylcytosin, VII, and 2-oxy-3-methyl-6-methylphenylamino-pyrimidin, VIII.



The remarkable tendency of certain pyrimidins to react with diazobenzene sulfonic acid, and the apparent inertness of the same ring in purins are of especial interest. According to Burian² substitution in the pyrimidin nucleus of purins did not influence the reaction with the diazo acid. While purins are closely related in structure to pyrimidins it is important to point out in this connection that positions 1 and 3 of the pyrimidin ring do not necessarily correspond to positions 1 and 3 in purins. While the pyrimidin nucleus is symmetrical, the purin, on the other hand, is unsymmetrical with respect to the 2 position. Two purins can theoretically be formed from a pyrimidin ring according as the glyoxalin ring is joined at the 4, 5 or 5, 6 positions. An inspection of the formulas below will show that this involves a change in the numbering of the atoms in the pyrimidin nucleus.



¹ Johnson and Clapp: *Loc. cit.*

² *Loc. cit.*

It is also of interest to note here that 6-oxypyrimidin¹ and 6-aminopyrimidin² do not give a red color with diazobenzene sulfonic acid. Whether this reagent reacts to form colored compounds only with pyrimidins having a —CO-NH— grouping in the 1, 2 or 2, 3 positions must be decided by further experiments.

The compounds formed by the action of diazobenzene sulfonic acid or pyrimidins appear to be more unstable than those formed in the case of purins. Two attempts to isolate the reaction-product in the case of thymin were unsuccessful.

The diazo acid used in our work was prepared according to the directions of Pauly.³ That the test shall not be found to be capricious it is absolutely necessary that the acid be pure and freshly prepared.

METHODS OF APPLYING THE TEST.

1. *With 10 per cent sodium hydroxide solution.*

Five to ten milligrams of the pyrimidin are dissolved in 0.5 cc. of 10 per cent sodium hydroxide solution and about 5.0 milligrams of diazobenzene sulfonic acid then added to the solution. If no reaction takes place the solution usually assumes a yellow or orange color. When a red color is formed it usually develops quite rapidly. The red color is usually quite permanent, lasting in some cases (thymin) for several hours.

2. *With $\frac{N}{10}$ sodium hydroxide solution.*

Dissolve 5.0 to 10.0 milligrams of the pyrimidin in 2 cc. of $\frac{N}{10}$ sodium hydroxide solution and add 5.0 to 10.0 milligrams of the sulfonic acid. This method of testing is not as reliable as Method 1.

3. *Testing on a watch glass.*

Five to ten milligrams of the pyrimidin and an equal weight of the sulfonic acid are mixed together, with a glass rod, on a dry

¹ Wheeler: *This Journal*, iii, p. 285, 1907.

² Büttner: *Ber. d. deutsch. chem. Gesellsch.*, xxxvi, p. 2232, 1903: Wheeler: *Loc. cit.*

³ *Zeitschr. f. physiol. Chem.*, xlii, p. 516.

watch glass. A drop of 10 per cent sodium hydroxide solution is then allowed to flow into the mixture. The red color develops immediately under these conditions. This method of applying the diazo test is recommended on account of its delicacy and reliability.

The results of our experiments are given, for comparison, in the following tables:

TABLE I.

Pyrimidins.	0.5 cc. 10 per cent NaOH solution.	2.0 cc. $\frac{N}{10}$ NaOH solution.	Test on watch-glass.
$\begin{array}{c} \text{NH} \text{---} \text{CO} \\ \qquad \\ \text{CO} \qquad \text{CCH}_3 \\ \qquad \\ \text{NH} \text{---} \text{CH} \\ \text{(Thymin).} \end{array}$	Intense red color, which disappears on diluting with water.	Light red which fades rapidly.	Intense red color.
$\begin{array}{c} \text{CH}_3\text{N} \text{---} \text{CO} \\ \qquad \\ \text{CO} \qquad \text{CCH}_3 \\ \qquad \\ \text{NH} \text{---} \text{CH} \\ \text{(1-Methylthymin.)} \end{array}$	Intense red color, which disappears on diluting with water.	No color.*	Intense red color.
$\begin{array}{c} \text{NH} \text{---} \text{CO} \\ \qquad \\ \text{CO} \qquad \text{CCH}_3 \\ \qquad \\ \text{CH}_3\text{N} \text{---} \text{CH} \\ \text{(3-Methylthymin.)} \end{array}$	No color.	No color.	No color.
$\begin{array}{c} \text{CH}_3\text{N} \text{---} \text{CO} \\ \qquad \\ \text{CO} \qquad \text{CCH}_3 \\ \qquad \\ \text{CH}_3\text{N} \text{---} \text{CH} \\ \text{(1, 3-Dimethylthymin.)} \end{array}$	No color.	No color.	No color.

*Note—The statement—*no color*—indicates that no red color was formed.

TABLE II.

Pyrimidins.	0.5 cc. 10 per cent NaOH solution.	2.0 cc. $\frac{N}{10}$ NaOH solution.	Test on watch-glass.
$\begin{array}{c} \text{NH} \text{---} \text{CO} \\ \quad \\ \text{CO} \quad \text{CH} \\ \quad \\ \text{NH} \text{---} \text{CH} \\ \text{(Uracil.)} \end{array}$	Red color but not as intense as with thymine.	Red color which developed slowly. Color permanent	Red color.
$\begin{array}{c} \text{CH}_3\text{N} \text{---} \text{CO} \\ \quad \\ \text{CO} \quad \text{CH} \\ \quad \\ \text{NH} \text{---} \text{CH} \\ \text{(1-Methyluracil).} \end{array}$	Red color.	Red color.	Red color.
$\begin{array}{c} \text{NH} \text{---} \text{CO} \\ \quad \\ \text{CO} \quad \text{CH} \\ \quad \\ \text{CH}_3\text{N} \text{---} \text{CH} \\ \text{(3-Methyluracil)} \end{array}$			
$\begin{array}{c} \text{CH}_3\text{N} \text{---} \text{CO} \\ \quad \\ \text{CO} \quad \text{CH} \\ \quad \\ \text{CH}_3\text{N} \text{---} \text{CH} \\ \text{(1, 3-Dimethyluracil).} \end{array}$	No color.	No color.	No color.

TABLE III.

Pyrimidins.	0.5 cc. 10 per cent NaOH solution.	2.0 cc. $\frac{N}{10}$ NaOH solution,	Test on watch-glass.
$ \begin{array}{c} \text{NH} \text{---} \text{CO} \\ \qquad \qquad \\ \text{CO} \qquad \text{CBr} \\ \qquad \qquad \\ \text{NH} \text{---} \text{CH} \\ \text{(5-Bromuracil.)} \end{array} $	Red color.	Faint red color which develops slowly.	Faint red color.
$ \begin{array}{c} \text{CH}_3\text{N} \text{---} \text{CO} \\ \qquad \qquad \\ \text{CO} \qquad \text{CBr} \\ \qquad \qquad \\ \text{NH} \text{---} \text{CH} \\ \text{(1-Methyl-5-bromuracil.)} \end{array} $	Red color.		
$ \begin{array}{c} \text{NH} \text{---} \text{CO} \\ \qquad \qquad \\ \text{CO} \qquad \text{CBr} \\ \qquad \qquad \\ \text{CH}_3\text{N} \text{---} \text{CH} \\ \text{(3-Methyl-5-bromuracil.)} \end{array} $	No color.	No color.	No color.
$ \begin{array}{c} \text{CH}_3\text{N} \text{---} \text{CO} \\ \qquad \qquad \\ \text{CO} \qquad \text{CBr} \\ \qquad \qquad \\ \text{CH}_3\text{N} \text{---} \text{CH} \\ \text{(1, 3-Dimethyl-5-bromuracil.)} \end{array} $	No color.	No color.	No color.

TABLE IV.

Pyrimidins.	0.5 cc. 10 per cent NaOH solution.	2.0 cc. $\frac{N}{10}$ NaOH solution.	Test on watch-glass.
$ \begin{array}{c} \text{N} = \text{C.NH}_2 \\ \quad \\ \text{CO} \quad \text{CH.H}_2\text{O} \\ \quad \\ \text{NH} - \text{CH} \\ \text{(Cytosin.)} \end{array} $	Red color which developed slowly.	Faint red.	Red color like uracil.
$ \begin{array}{c} \text{N} = \text{CNH}_2 \\ \quad \\ \text{CO} \quad \text{CH} \\ \quad \\ \text{CH}_3\text{N} - \text{CH} \\ \text{(3-Methyl-cytosin.)} \end{array} $	No color.	No color.	No color.
$ \begin{array}{c} \text{N} = \text{CN} \begin{array}{l} \nearrow \text{CH}_3 \\ \searrow \text{C}_6\text{H}_5 \end{array} \\ \quad \\ \text{CO} \quad \text{CH} \\ \quad \\ \text{NH} - \text{CH} \end{array} $	Red color.	No color.	Red color.
$ \begin{array}{c} \text{N} = \text{CN} \begin{array}{l} \nearrow \text{CH}_3 \\ \searrow \text{C}_6\text{H}_5 \end{array} \\ \quad \\ \text{CO} \quad \text{CH} \\ \quad \\ \text{CH}_3\text{N} - \text{CH} \end{array} $	No color.	No color.	No color.

TABLE V.

Pyrimidins.	0.5 cc. 10 per cent NaOH solution.	2.0 cc. $\frac{N}{10}$ NaOH solution.	Test on watch-glass.
$ \begin{array}{c} \text{N} = \text{CNH}_2 \\ \quad \\ \text{CO} \quad \text{CCH}_3 \\ \quad \\ \text{NH} - \text{CH} \end{array} $ (5-Methyl-cytosin)	Intense red color.	Faint red which faded.	Intense red.
$ \begin{array}{c} \text{N} = \text{CNH}_2 \\ \quad \\ \text{CO} \quad \text{CCH}_3 \\ \quad \\ \text{CH}_3\text{N} - \text{CH} \end{array} $ (3, 5-Dimethyl-cytosin.)	No color.	No color.	No color.

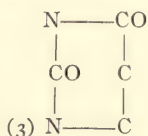
SUMMARY.

(1) Thymin, uracil and cytosin react with diazobenzene sulfonic acid, in presence of alkali, giving red colored solutions.

(2) The color is given by thymin with greater intensity than by uracil and cytosin.

(3) Substitution in position 3 of the pyrimidin ring prevents the formation of a red color.

(4) Accepting the statement of Burian,¹ that nucleic acids do not react with diazobenzene sulfonic acid, the foregoing observations seem to indicate that thymin and probably uracil and cytosin as well are linked in nucleic acids at position 3.



(5) Whether the pyrimidins are linked to phosphorus, a carbohydrate complex or otherwise must be decided by further study.

Ber. d. deutsch. chem. Gesellsch., xxxvii, p. 708; *Zeitschr. f. physiol. Chem.*, li, p. 435.

[Reprinted from the American Chemical Journal, Vol. XL.
No. 2. August, 1908.]

[Contributions from the Sheffield Laboratory of Yale University.]

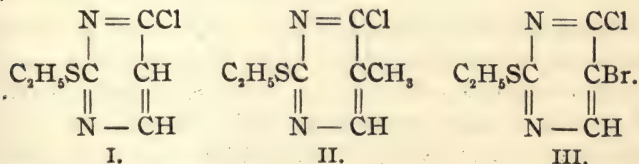
CLVII.—RESEARCHES ON PYRIMIDINES: THE ACTION OF POTASSIUM THIOCYANATE UPON SOME IMIDECHLORIDES.

[THIRTY-FIFTH PAPER.]

BY TREAT B. JOHNSON AND WALTER F. STOREY.

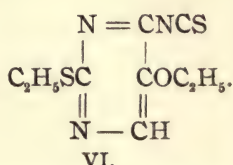
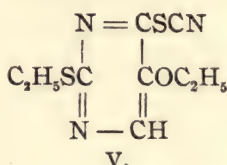
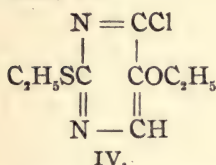
Two papers entitled "The Action of Potassium Thiocyanate upon Imidechlorides" have previously been published from this laboratory.

In the first paper¹ the authors showed that the three imidechlorides, *viz.*, 2-ethylmercapto-6-chlorpyrimidine, I., 2-ethylmercapto-5-methyl-6-chlorpyrimidine, II., and 2-ethylmercapto-5-brom-6-chlorpyrimidine, III., reacted with potassium thiocyanate, under certain conditions, giving isothiocyanates. They made no attempts to obtain evidence of the intermediate formation of thiocyanates.

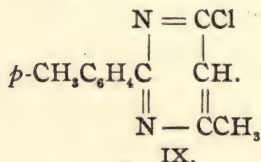
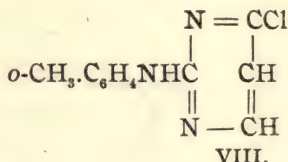
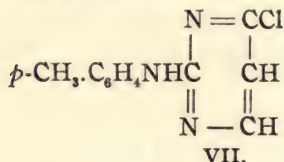


¹ Wheeler and Bristol: THIS JOURNAL, 33, 448.

In the second paper,¹ Johnson and McCollum described an unique case of the molecular rearrangement of a thiocyanate into an isothiocyanate. They observed that 2-ethylmercapto-5-ethoxy-6-chlorpyrimidine, IV., reacted, in alcohol, with potassium thiocyanate, giving 2-ethylmercapto-5-ethoxy-6-thiocyanpyrimidine, V., which then underwent a metameric change into 2-ethylmercapto-5-ethoxy-6-isothiocyanpyrimidine, VI.



The work described in this paper was undertaken with the object of examining the behavior of potassium thiocyanate towards the three cyclic imidechlorides, *viz.*, 2-paratoluidino-6-chlorpyrimidine, VII., 2-orthotoluidino-6-chlorpyrimidine, VIII., and 2-paratolyl-4-methyl-6-chlorpyrimidine, IX. Incidentally we have also reinvestigated the action of potassium thiocyanate on the imidechlorides, I., II., and III., studied by Wheeler and Bristol.

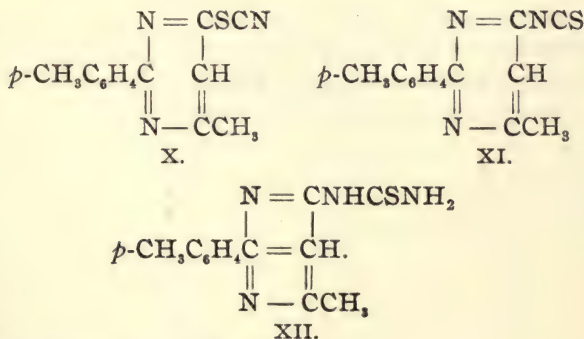


2-Paratoluidino-6-chlorpyrimidine, VII., and 2-orthotoluidino-6-chlorpyrimidine, VIII., were prepared from 2-ethylmercapto-6-oxypyrimidine. This mercaptopyrimidine reacted, in a smooth manner, with *para*- and *ortho*toluidine, at 100°, giving quantitative yields of 2-paratoluidino-6-oxypyrimidine

¹ THIS JOURNAL, 36, 136.

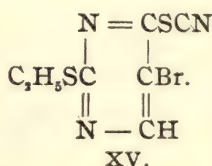
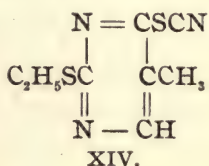
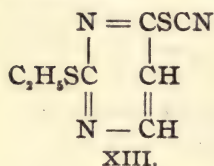
and 2-orthotoluidino-6-oxypyrimidine, respectively. The oxypyrimidines were then converted into the imidechlorides, VII. and VIII., by treatment with phosphorus oxychloride or phosphorus pentachloride. These two chlorides are more stable in alcoholic solutions than the corresponding 2-ethyl-mercapto-6-chloropyrimidine. While the mercapto derivative is decomposed by boiling alcohol the toluidinopyrimidines can be recrystallized repeatedly from this solvent without alteration. We now find that these two chlorides do not react with potassium thiocyanate under normal conditions. They were recovered unaltered after digesting, in alcohol or acetone, with potassium thiocyanate for several hours.

On the other hand, 2-paratolyl-4-methyl-6-chloropyrimidine, IX., which was obtained from 2-paratolyl-4-methyl-6-oxypyrimidine¹ by the action of phosphorus pentachloride, reacted in a smooth manner with potassium thiocyanate, giving a good yield of 2-paratolyl-4-methyl-6-thiocyanpyrimidine, X. This thiocyanate was stable at ordinary temperature and reacted with thiobenzoic acid, giving a quantitative yield of 2-paratolyl-4-methyl-6-thiopyrimidine. When heated above its melting point, the thiocyanate was converted into a mixture of the isothiocyanate, XI., and apparently a polymeric form of the isothiocyanate melting at 204°. The isothiocyanate reacted with aqueous ammonia at ordinary temperature, giving 2-paratolyl-4-methyl-6-thioureaprimidine, XII.



¹ Glock: Ber. d. chem. Ges., **21**, 2658.

Wheeler and Bristol,¹ in their investigation of the action of potassium thiocyanate on the imidechlorides, 2-ethylmercapto-6-chlorpyrimidine, I., 2-ethylmercapto-5-methyl-6-chlorpyrimidine, II., and 2-ethylmercapto-5-brom-6-chlorpyrimidine, III., worked with the object of converting these chlorides into isothiocyanates. They invariably digested the chlorides with potassium thiocyanate in toluene or alcohol for 3 to 15 hours. Under these conditions the thiocyanates, if formed, would be converted completely into isothiocyanates. We now find that these imidechlorides give practically quantitative yields of the thiocyanates XIII., XIV., and XV., when warmed in alcohol with potassium thiocyanate, if the time of digestion is limited to 20 to 60 minutes. The thiocyanates are stable at ordinary temperature and can be recrystallized from alcohol without alteration. They rearrange smoothly into isothiocyanates when heated above their melting points or when digested for long periods with alcohol. The isothiocyanates, when formed under the latter condition, react with the alcohol, giving the corresponding 6-thiourethane-pyrimidines:



The melting points and boiling points of all the 6-thiocyanpyrimidines, 6-isothiocyanpyrimidines, and corresponding 6-thioureapypyrimidines, which have been prepared in this laboratory, are given in the following table:

¹ *Loc. cit.*

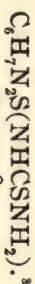
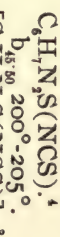
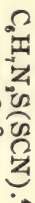
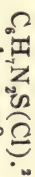
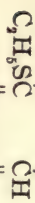
6-Oxypyrimidines.



6-Chloropyrimidines. 6-Thiocyanpyrimidines.

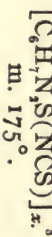
6-Isothiocyanpyrimidines.

6-Thioureapyrimidines.



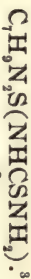
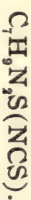
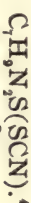
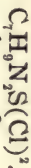
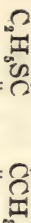
b_4 135°.

m. 82°.



m. 214°.

m. 152°.

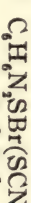
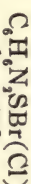
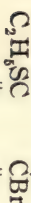


b_{25} 157°.

m. 95°.

m. 192°.

m. 159°.



b_{26} 168°.

m. 81°-82°.

m. 220°.

m. 189°.

¹ Wheeler and Merriam: THIS JOURNAL, 29, 484.

² Wheeler and Johnson: *Ibid.*, 29, 492; 31, 591.

³ Wheeler and Bristol: *Ibid.*, 33, 448.

⁴ This paper.

6-Oxypyrimidines.

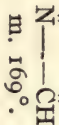
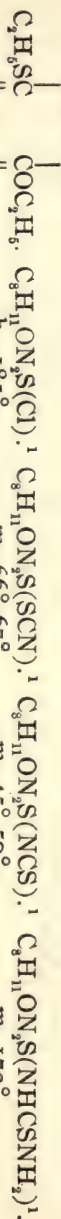


6-Chloropyrimidines.

6-Thiocyanopyrimidines.

6-Isothiocyanopyrimidines.

6-Thioureapyrimidines.

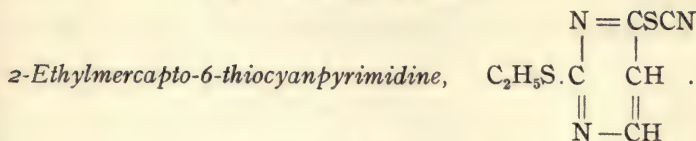


¹ Johnson and McCollum: THIS JOURNAL, **36**, 136; J. Biolog. Chem., **1**, 437.

² Loc. cit.

³ This paper.

EXPERIMENTAL PART.



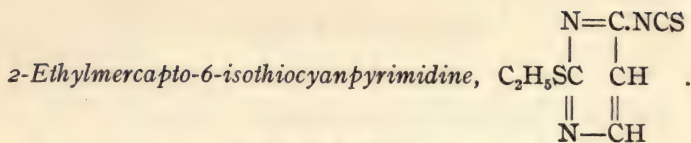
BY DR. E. V. MCCOLLUM.

Three and nine-tenths grams of potassium thiocyanate were dissolved in 40 cc. of 95 per cent alcohol and 7 grams of 2-ethylmercapto-6-chlorpyrimidine added to the solution. There was an immediate reaction with separation of potassium chloride. The mixture was warmed on the steam bath for twenty minutes and the insoluble potassium chloride separated by filtration. On cooling the alcohol solution, the thiocyanate deposited in prismatic crystals which were purified for analysis by recrystallization from alcohol. It separated in aggregates of rectangular prisms melting without effervescence at 82° to a clear oil. The compound was insoluble in alkali and did not react with ammonia or aniline at 100°. Analysis (Kjeldahl):

	Calculated for $\text{C}_7\text{H}_7\text{N}_3\text{S}_2$.	Found.		
		I.	II.	III.
N	21.31	20.89	21.32	21.09

When the alcohol filtrates were combined and evaporated to dryness a yellow, crystalline residue was obtained which partially dissolved in cold 10 per cent solution of sodium hydroxide. When this solution was acidified with acetic acid we obtained 0.3 gram of material which crystallized from alcohol in flat prisms or plates melting at 92°–93°. The compound was identical with the 2-ethylmercapto-6-thionethylurethanepyrimidine described by Wheeler and Bristol.¹ A quantitative yield of the above thiocyanate can be obtained by boiling 2-ethylmercapto-6-chlorpyrimidine in acetone solution with potassium thiocyanate. It was very soluble in acetone and separated in prismatic crystals melting at 81°–82°.

¹ *Loc. cit.*

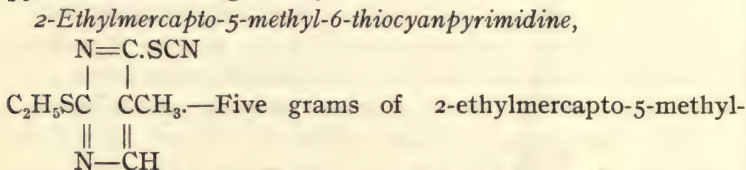


BY DR. F. V. MCCOLLUM.

2-Ethylmercapto-6-thiocyanpyrimidine shows no tendency to rearrange to the isothiocyanate at ordinary temperature. On the other hand, a rearrangement took place when the thiocyanate was heated for 4 to 5 hours at 80° – 90° . The isothiocyanate was obtained as an oil which reacted at once with aniline, giving 2-ethylmercapto-6-phenylthiourea-pyrimidine¹ melting at 205° .

The isothiocyanate was obtained as a yellow oil boiling at 200° – 205° (45–50 mm.) when the thiocyanate was distilled. It did not crystallize on standing but a yellow, crystalline compound slowly deposited. This was difficultly soluble in benzene and practically insoluble in alcohol. It melted at 175° – 177° and did not react with ammonia. The compound is apparently identical with the product which Wheeler and Bristol obtained by treating 2-ethylmercapto-6-chlorpyrimidine with potassium thiocyanate. It is probably a polymeric form of the isothiocyanate, $(\text{C}_7\text{H}_7\text{N}_3\text{S}_2)_x$.

The isothiocyanate reacted at once with aqueous ammonia, with evolution of heat, giving 2-ethylmercapto-6-thiourea-pyrimidine² melting at 214° .



6-chlorpyrimidine and 3.5 grams of dry potassium thiocyanate were dissolved in 25 cc. of absolute alcohol and the solution boiled for 1 hour. The undissolved potassium chloride was then filtered off and the solution evaporated on the steam bath. We obtained a syrup which was triturated with cold water to remove any potassium chloride and then extracted

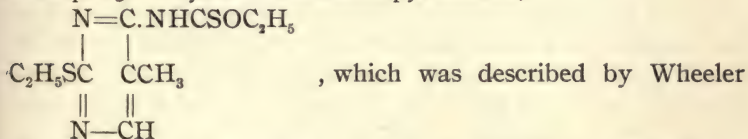
¹ Wheeler and Bristol: *Loc. cit.*² *Ibid.*

with ether. When the ether was evaporated we obtained an oil which did not solidify after standing for several days. This oil partially dissolved in 10 per cent sodium hydroxide. The insoluble portion solidified on standing, and crystallized from 95 per cent alcohol in beautiful prisms melting without effervescence at 95° to a clear oil. It did not react with ammonia or aniline and a nitrogen determination agreed with the calculated value for a thiocyanate (Kjeldahl):

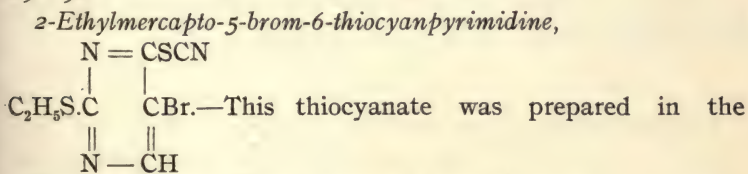
	Calculated for $C_8H_9N_3S_2$.	Found.
N	19.90	19.6

The thiocyanate dissolved at once in cold thioacetic acid without apparent evolution of heat. On standing, beautiful prismatic crystals deposited which melted at 179° – 180° . This compound was not examined further but it probably was *2-ethylmercapto-5-methyl-6-thiopyrimidine*. It dissolved in alkalis and gave a test for sulphur.

When the sodium hydroxide solution (above) was acidified with acetic acid we obtained an oil which soon solidified. It was insoluble in water but crystallized from 95 per cent alcohol in stout prisms melting at 90° . It was identical with *2-ethylmercapto-5-methyl-6-thionurethanepyrimidine*,



and Bristol.¹ A mixture of the two compounds melted at 89° – 90° .



This thiocyanate was prepared in the following manner: Five grams of *2-ethylmercapto-5-brom-6-chlorpyrimidine* and 2.5 grams of potassium thiocyanate were dissolved in 50 cc. of 95 per cent alcohol and the solution boiled on the steam bath for 20 minutes. The insoluble potassium

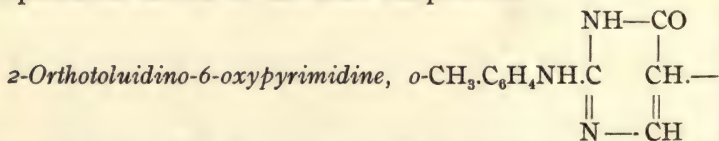
¹ Loc. cit.

chloride was filtered off and the filtrate cooled, when the thiocyanate deposited in prisms melting at 81° – 82° . They were very soluble in acetone, boiling ligroin, warm alcohol, and benzene. The compound did not dissolve in sodium hydroxide and could be warmed with ammonia without alteration. Analysis (Kjeldahl):

	Calculated for $C_7H_6N_3S_2Br$.	I.	Found.	II.
N	15.21	15.32		15.28

Action of Thioacetic And Thiobenzoic Acids On 2-Ethylmercapto-5-brom-6-thiocyanpyrimidine.—About 0.3 gram of the thiocyanate was dissolved in a small quantity of thioacetic acid. Reaction took place at once, on warming, without evolution of carbon bisulphide, giving large, well-developed prisms. The compound crystallized from benzene in rhombic prisms that melted at 198° with slight effervescence. It was identified as 2-ethylmercapto-5-brom-6-thiopyrimidine.¹ A mixture of the two products melted at the same temperature. The same 6-thiopyrimidine was obtained when the thiocyanate was warmed in a water bath with a molecular proportion of thiobenzoic acid.

Rearrangement of 2-Ethylmercapto-5-brom-6-thiocyanpyrimidine into the Isothiocyanate.—About 0.2 gram of the thiocyanate was heated for 2 hours at 150° – 160° . We obtained a red oil which solidified on cooling and melted at 75° – 80° . That a rearrangement had taken place was shown in the following manner: The compound (melting at 75° – 80°) reacted at once with ammonia, giving 2-ethylmercapto-5-brom-6-thiourea-pyrimidine² melting at 219° – 220° . A mixture of the two preparations melted at the same temperature.



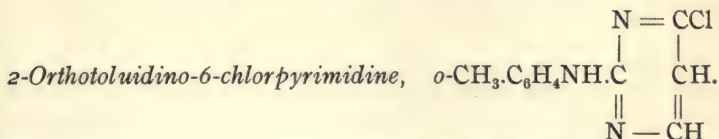
Eighteen grams of 2-ethylmercapto-6-oxypyrimidine and one molecular proportion of orthotoluidine (14 grams) were heated together on the steam bath for 3 days. The evolution of

¹ Wheeler and Bristol: *Loc. cit.*

² *Ibid.*

mercaptan was then complete and a compound was obtained which was difficultly soluble in alcohol. It crystallized from hot alcohol or acetic acid in prismatic crystals melting at 219° – 220° . It was soluble in alkali. Analysis (Kjeldahl):

	Calculated for $C_{11}H_{11}ON_3$.	Found.	
		I.	II.
N	20.89	20.93	20.74



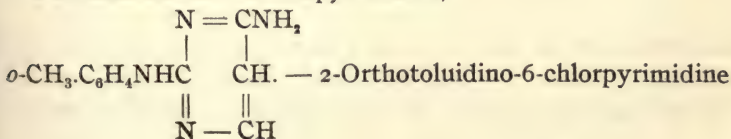
—Ten grams of 2-orthotoluidino-6-oxypyrimidine were heated on the steam bath with 25 cc. of phosphorus oxychloride until the evolution of hydrochloric acid gas ceased. The excess of phosphorus oxychloride was then distilled under diminished pressure. We obtained a yellow oil, which assumed a crystalline form when treated with ammonia. The compound crystallized from alcohol in corpuscular crystals melting at 78° . It was insoluble in alkali. Analysis (Kjeldahl):

	Calculated for $C_{11}H_{10}N_3Cl$.	Found.	
		I.	II.
N	19.1	18.8	18.92

Action of Potassium Thiocyanate on 2-Orthotoluidino-6-chlorpyrimidine:—Four grams of the chlorpyrimidine and 3 grams of potassium thiocyanate were dissolved in 50 cc. of alcohol and the solution boiled for 2 hours. After filtering a small amount of insoluble material the excess of alcohol was evaporated on the steam bath. We obtained a crystalline residue which crystallized from alcohol and melted at 77° – 78° . It responded to a test for chlorine and was identified as the unaltered chloride. Analysis (Kjeldahl):

	Calculated for $C_{11}H_{10}N_3Cl$.	Found.
N	19.1	19.07

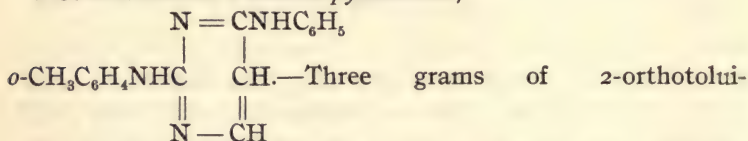
2-Orthotoluidino-6-aminopyrimidine,



does not react with ammonia at ordinary temperature. When heated with alcoholic ammonia for 2 hours at 140° – 150° it gave a quantitative yield of the aminopyrimidine. This was very soluble in alcohol and crystallized from dilute alcohol in aggregates of small prisms melting at 124° . Analysis (Kjeldahl):

	Calculated for $C_{11}H_{12}N_4$.	Found.
N	28.00	27.7

2-Orthotoluidino-6-anilinopyrimidine,

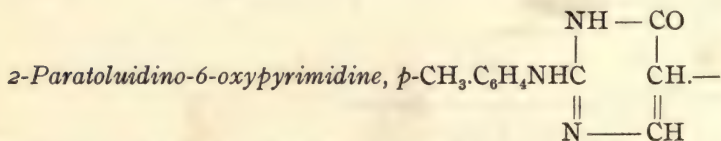


dino-6-chlorpyrimidine and 4 grams of aniline were dissolved in 25 cc. of benzene and the solution boiled for 6 hours. It was then filtered and evaporated to dryness. We obtained a crystalline residue which was washed with water to remove aniline hydrochloride and then dissolved in warm dilute hydrochloric acid. The hydrochloride of the anilinopyrimidine crystallized, on cooling, in slender needles melting at 126° . Analysis (Kjeldahl):

	Calculated for $C_{17}H_{16}N_4 \cdot \text{HCl}$.	Found.
N	17.92	17.73

When the hydrochloride was dissolved in water and ammonia added to the solution the free base separated. It crystallized from dilute alcohol in hexagonal plates melting at 128° to a clear oil. Analysis (Kjeldahl):

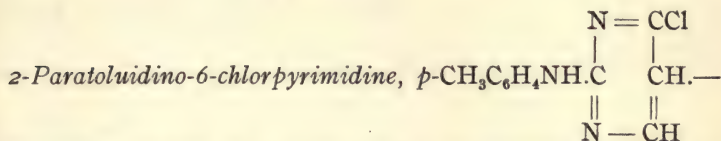
	Calculated for $C_{17}H_{16}N_4$.	Found.
N	20.28	20.29



This compound is formed, in a smooth manner, by heating 2-ethylmercapto-6-oxyprymidine with a molecular proportion of paratoluidine at 100° . It was difficultly soluble in warm alcohol, acetone, boiling water, and cold acetic acid. It crystal-

lized from acetic acid in clusters of needles melting at 270° – 271° . Analysis (Kjeldahl):

	Calculated for $C_{11}H_{11}ON_3$.	Found.
N	20.89	21.0

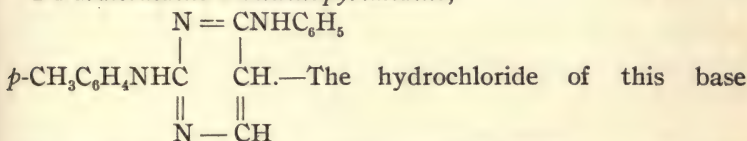


Twenty-six grams of 2-paratoluidino-6-oxypyrimidine were digested with 65 cc. of phosphorus oxychloride until the evolution of hydrochloric acid gas ceased. We obtained a dark colored solution which was heated at 100° under diminished pressure to remove the excess of phosphorus oxychloride. The residue was dissolved in ice water and the solution made alkaline with ammonia when the chlorpyrimidine deposited. It crystallized from alcohol in prisms melting at 112° – 113° to an oil. Analysis (Kjeldahl):

	Calculated for $C_{11}H_{10}N_3Cl$.	Found.
N	19.13	18.99

Action of Potassium Thiocyanate on 2-Paratoluidino-6-chlorpyrimidine:—This pyrimidine was recovered unaltered, melting at 112° – 113° , after warming, in acetone solution, with potassium thiocyanate for 2.5 hours.

2-Paratoluidino-6-anilinopyrimidine,



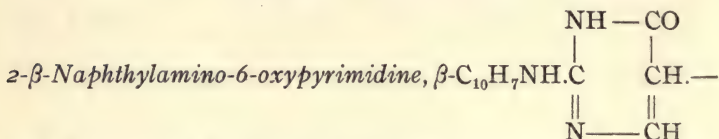
The hydrochloride of this base was obtained when 2-paratoluidino-6-chlorpyrimidine was warmed in benzene with aniline. The salt was very soluble in hot water and alcohol. It crystallized from alcohol in prisms which decomposed at 134° . Analysis (Kjeldahl):

	Calculated for $C_{17}H_{16}N_4\cdot\text{HCl}$.	Found.
N	17.92	17.96

When sodium hydroxide was added to an aqueous solution of this salt the pyrimidine base deposited in needles. It was

insoluble in hot water, and crystallized from alcohol in needles melting at 135° to an oil. Analysis (Kjeldahl):

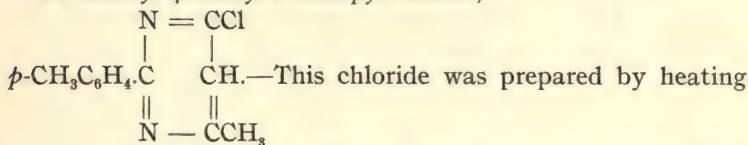
	Calculated for $C_{17}H_{16}N_4$.	Found.
N	20.28	20.15



From β -naphtylamine and 2-ethylmercapto-6-oxy-pyrimidine. It was insoluble in hot water and difficultly soluble in alcohol. It crystallized from alcohol in clusters of needles melting at 270° . Analysis (Kjeldahl):

	Calculated for $C_{14}H_{11}ON_3$.	Found.
N	17.72	17.77

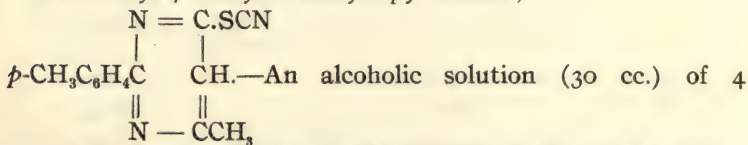
2-Paratolyl-4-methyl-6-chlorpyrimidine,



on the steam bath 15 grams of 2-paratolyl-4-methyl-6-oxy-pyrimidine¹ with 17 grams of phosphorus pentachloride and about 20 cc. of phosphorus oxychloride for 7 hours. A dark colored solution was obtained which was slowly poured upon crushed ice to destroy the phosphorus halides. The chlorpyrimidine separated at once, and crystallized from alcohol in beautiful prisms melting at 107° to a clear oil. Analysis (Kjeldahl):

	Calculated for $C_{13}H_{11}N_3\text{Cl}$.	I.	Found.	II.
N	12.81	12.75		12.83

2-Paratolyl-4-methyl-6-thiocyanpyrimidine,



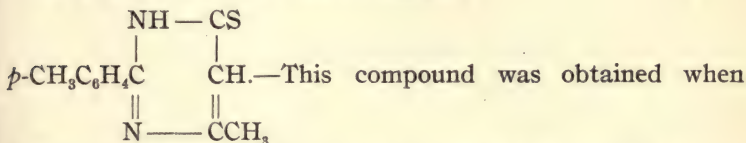
grams of 2-paratolyl-4-methyl-6-chlorpyrimidine and 3 grams

¹ *Loc. cit.*

of potassium thiocyanate was boiled for 1.5 hours. The insoluble potassium chloride was removed by filtration, and the solution cooled, when the thiocyanate separated in irregular prisms. It crystallized from alcohol in fern-shaped crystals melting at 123° . When warmed with aniline or aqueous ammonia at 100° it was recovered unaltered. Analysis (Kjeldahl):

	Calculated for $C_{19}H_{11}N_3S$.	Found.
N	17.42	17.2

2-Paratolyl-4-methyl-6-thiopyrimidine,



2-paratolyl-4-methyl-6-thiocyanpyrimidine was gently warmed with one molecular proportion of thiobenzoic acid. It deposited from alcohol in slender prisms melting at 114° . Analysis (Kjeldahl):

	Calculated for $C_{12}H_{12}N_2S$.	Found.
N	12.96	12.81

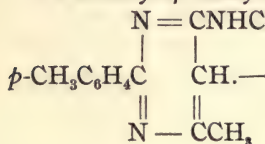
Rearrangement of 2-Paratolyl-4-methyl-6-thiocyanpyrimidine into the Isothiocyanate.—One and five-tenths grams of the thiocyanate were heated, in an oil bath, for 2.5 hours at 130° – 135° . We obtained a thick oil which slowly crystallized after cooling. The compound was very soluble in warm alcohol and on cooling crystallized in radiating prisms melting at 207° – 208° . It did not react with ammonia and a nitrogen determination agreed with the calculated value for the isothiocyanate. It probably is a polymeric form of the isothiocyanate, $(C_{13}H_{11}N_3S)_x$. Analysis (Kjeldahl):

	Calculated for $(C_{13}H_{11}N_3S)_x$.	Found.
N	17.42	17.35

In a second experiment the thiocyanate was heated for 2 hours at 130° – 135° , cooled, and then suspended in aqueous ammonia for 2 days. We obtained a yellow amorphous pro-

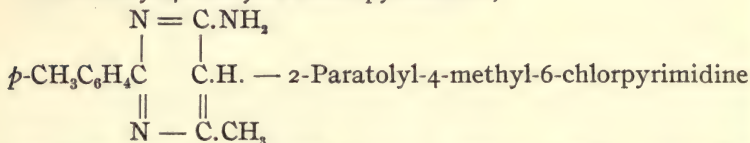
duct which crystallized from alcohol in irregular prisms melting at 145° – 146° . A nitrogen determination agreed with the calculated value for

2-Paratolyl-4-methyl-6-thioureapyrimidine,



	Calculated for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{S}$.	Found.
N	21.70	21.45

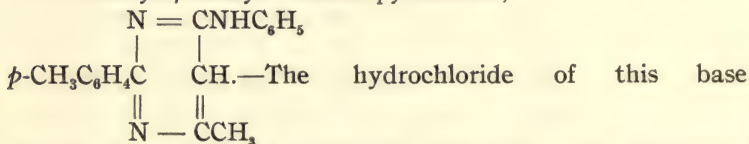
2-Paratolyl-4-methyl-6-aminopyrimidine,



was recovered unaltered after heating with alcoholic ammonia for 2 hours at 120° and again for 2 hours at 150° – 160° . When heated with ammonia at 180° – 190° for 2 hours a good yield of the aminopyrimidine was obtained. It deposited from alcohol in hexagonal tables melting at 178° – 179° . Analysis (Kjeldahl):

	Calculated for $\text{C}_{12}\text{H}_{13}\text{N}_3$.	Found.
N	21.10	21.06

2-Paratolyl-4-methyl-6-anilinopyrimidine,



was obtained when 1 gram of 2-paratolyl-4-methyl-6-chloropyrimidine and 1 gram of aniline were warmed in benzene for 6 hours. The salt crystallized from alcohol in clusters of needles melting at 269° – 270° with effervescence. Analysis (Kjeldahl):

	Calculated for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{.HCl}$.	Found.
N	13.48	13.44

The base crystallized from alcohol in needles melting at 120°-121° to an oil. Analysis (Kjeldahl):

Calculated for $C_{18}H_{17}N_3$.		Found.
N	15.27	15.17

NEW HAVEN, CONN.,
March 1, 1908.

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CLVIII. — RESEARCHES ON PYRIMIDINES: SYN-
THESIS OF CYTOSINE-5-CARBOXAMIDE.

[THIRTY-SIXTH PAPER.¹]

BY HENRY L. WHEELER AND CARL O. JOHNS.

In our previous papers on the synthesis of the 5-carboxyl derivatives of uracil² and cytosine³ we have shown that Claisen's ethoxymethylenemalonic ester,⁴ $C_2H_5OCH = C(CO_2C_2H_5)_2$,

¹ A complete list of our previous papers on pyrimidines up to the end of the year 1907 is given at the end of this article.

² THIS JOURNAL, **37**, 392 (1907).

³ *Ibid.*, **38**, 594 (1907).

⁴ Ann. Chem. (Liebig), **297**, 75 (1897).

condenses in alkaline solution with 2-ethylpseudothiurea, $\text{H}_2\text{N}-\text{C}(\text{SC}_2\text{H}_5)=\text{NH}$, giving 2-ethylmercapto-5-carbethoxy-6-oxypyrimidine (Formula I., on page 237). The condensation is especially smooth. We have succeeded in greatly increasing the yield of pyrimidine over the amount obtained in our first experiments and this condensation now offers an excellent starting point for further syntheses. We have also previously shown that 2-ethylmercapto-5-carbethoxy-6-oxypyrimidine is easily saponified by alkali and the yield of 2-ethylmercapto-6-oxypyrimidine-5-carboxylic acid, II., is very good.

We now find that with proper precautions this mercapto acid can be practically quantitatively converted into the acid chloride of 2-ethylmercapto-6-chlorpyrimidine-5-carboxylic acid, III. This acid chloride is a very reactive substance and, as might be expected, the chlorine attached to the CO group is more reactive than that in the 6 position.

When the dichloride is treated with cold aqueous ammonia one chlorine atom is replaced by the amino group and 2-ethylmercapto-6-chlorpyrimidine-5-carboxamide, IV., results. This is proved by the fact that on treating the chloramide with sodium ethylate an ethoxy derivative, V., is obtained which is isomeric and not identical with 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine, X.

When the dichlorpyrimidine is warmed with concentrated aqueous ammonia on the steam bath, both chlorine atoms are removed and it is quantitatively converted into 2-ethylmercapto-6-aminopyrimidine-5-carboxamide, VI.

We have found that this acid amide combines with bromine with the evolution of heat and that the product has the properties and composition of a dibrom addition product, VII. When it was treated with alkali it regenerated unaltered 2-ethylmercapto-6-aminopyrimidine-5-carboxamide.

When it was heated under certain conditions, its loss in weight and percentage of nitrogen corresponded with that required for the formation of a monobromamide. If a monobromamide was formed here it might be expected that, in common with such substances, on treatment with alkali the bromamide group, RCONHBr , would undergo a rearrange-

ment into the carbonamide form, RNCO. In this case the reactive grouping would probably unite with the adjacent amino group in the 6 position, forming a five membered ring, with the result that an 8-oxypurine would be obtained.

When the product or mixture obtained by heating the dibrom addition product was treated with aqueous alkali, cytosine-5-carboxylic acid, VIII., sometimes 2-ethylmercapto-6-aminopyrimidine-5-carboxamide, VI., and a product free from sulphur was obtained. This latter substance and its salts gave results on analysis which closely agreed with the calculated for 2,8-dioxypurine, XI., the only one of the dioxypurines that has not been described. The empirical formula of 2,8-dioxypurine, $C_5H_4O_2N_4$, differs from cytosine-5-carboxamide, IX., $C_5H_6O_2N_4$, by only two hydrogen atoms. The percentage composition of these substances is therefore so closely similar that the analysis did not decide which one of the two we were dealing with. In our previous work we had reason to believe that we had obtained cytosine-5-carboxamide, IX. With the object of preparing this substance, the behavior of the ethyl ester of cytosine-5-carboxylic acid, or 5-carbethoxycytosine, XII., with aqueous ammonia was examined at that time and it was found that this ether showed an exceptional inertness. On heating at 140° to 150° for two hours, about 25 per cent remained unaltered. On concentrating the mother liquor more soluble material crystallizing in needles was obtained. The analytical results in this case and the method of preparation were then taken to indicate that the expected cytosine-5-carboxamide had been obtained. Owing to the poor yield, nothing further was done with this substance.

This material was not identical with that obtained in the present work. The facts then seemed to show that the material obtained from the brom addition product, VII., was 2,8-dioxypurine. The question was finally settled in the negative, as follows: The material obtained by heating the dibromamide and then treating with alkali was carefully freed from 2-ethylmercapto-6-aminopyrimidine-5-carboxamide and cytosine-5-carboxylic acid. It was then boiled with strong hydrochloric acid and found to completely decompose into cytosine-5-carboxylic acid.

This shows that no Hofmann rearrangement had taken place and that the present substance is the true cytosine-5-carboxamide.

The inertness of 5-carbethoxycytosine, and also of 2,6-diamino-5-carbethoxypyrimidine,¹ on heating with ammonia, is comparable with that of the dialkylmalonic esters.² The ammonium salts of these acids break down with the evolution of carbon dioxide, and since 5-carbethoxycytosine is a substituted malonic acid derivative this offers an explanation of our previous results. The material formerly viewed as cytosine-5-carboxamide was probably impure or partly hydrous cytosine.

It is probable that no monobromamide was formed on heating the dibrom addition product and that the dibrom addition product has the bromine atoms attached to the double bond between the 4 and 5 positions. Similar additions of bromine to the double bond have been observed in other cases in this laboratory, *e. g.*, thymine and 4,5-dimethyluracil. The compounds in general have little stability. An unusually stable dibrom addition product of this sort, prepared from 2-phenylhydrazine-4-methyl-6-oxypyrimidine, has been described by Pellizzari and Roncagliolo.³

When 2-ethylmercapto-6-aminopyrimidine-5-carboxamide, VI., was boiled with hydrochloric acid it was converted into cytosine-5-carboxylic acid. When given a less energetic treatment with acid, in addition to unaltered material, some cytosine-5-carboxamide along with cytosine-5-carboxylic acid was obtained. This amide was identical with that obtained from the brom product.

The question whether or not the Hofmann rearrangement can be applied in the pyrimidine series still remains to be investigated. A 2-oxygen amide such as cytosine-5-carboxamide, being soluble in alkali and free from sulphur, would be a more promising substance than the mercaptoamide to decide this question. The work will be undertaken as soon

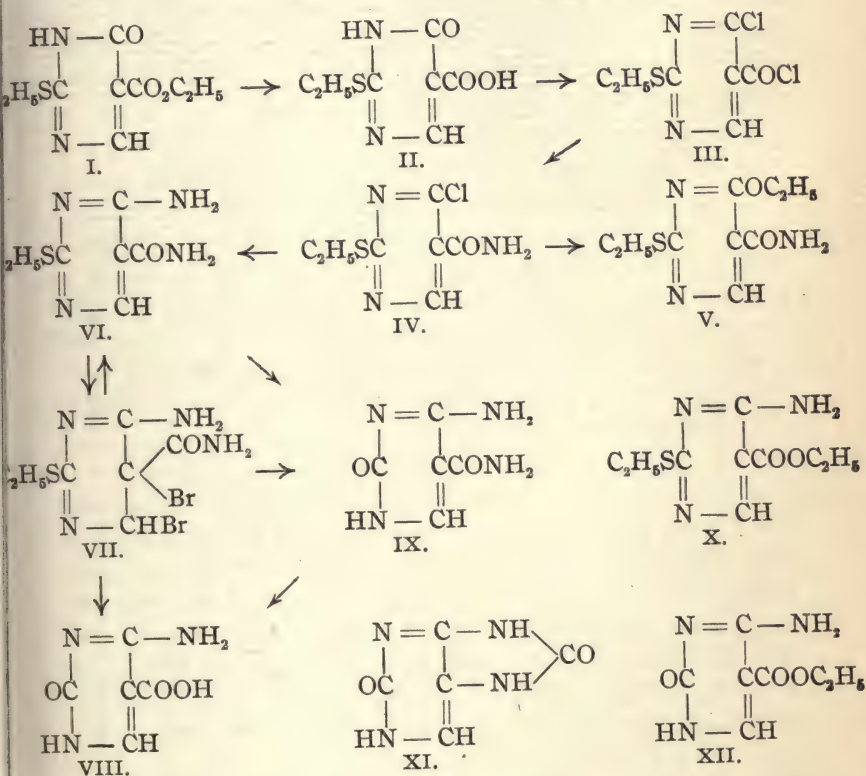
¹ THIS JOURNAL, **38**, 598 (1907).

² Fischer and Diltthey: Ber. d. chem. Ges., **35**, 844.

³ Gaz. chim. ital., **31**, I, 513.

as a more convenient method of preparing this amide, in quantities sufficient for synthetical purposes, is obtained.

It appears from the above results that the unsaturated condition of the molecule, or the double bond in the 4,5 position, interferes with the Hofmann rearrangement, at least in the case of 2-ethylmercapto-6-aminopyrimidine-5-carboxamide.



EXPERIMENTAL PART.

Ethoxymethylenemalonic Ester, $\text{C}_2\text{H}_5\text{OCH}=\text{C}(\text{CO}_2\text{C}_2\text{H}_5)_2$. — Since this ester has proved to be of special importance for pyrimidine syntheses a detailed account is given of our methods of preparing and employing the substance.

The ester was prepared essentially according to Claisen's directions.¹ We have found that the mixture of malonic ester (100 grams), orthoformic ester (93 grams), acetic anhydride (128 grams), and zinc chloride (7 grams) reacts immediately on gently warming and enough heat is evolved to boil the solution. The mixture was kept boiling for an hour, then all that distilled up to 110° at ordinary pressure (the bulb of the thermometer being *in the solution*) was removed. The distillate usually weighed about 52 grams and represented the ethyl acetate formed in the reaction. A little anhydride was usually carried over.

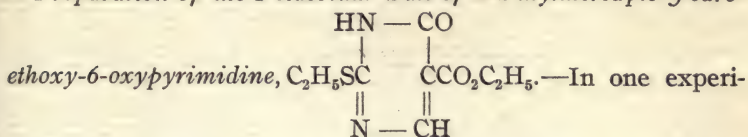
It was found that it is unnecessary to boil the above mixture for 11–12 hours, as stated by Claisen. In fact, heating the flask attached to a return condenser in an oil bath at 120° – 130° , or so that the mixture boiled gently, for two more hours was sufficient. There were then obtained 14–15 grams of impure ethyl acetate or about 67 grams in all, which is 60 per cent of the calculated. The calculated yield of ethyl acetate is 110 grams. Boiling for a longer time gave very little more ethyl acetate. A portion of the ethyl acetate, however, probably remains behind in the mixture.

The mixture was then distilled at 15–20 mm. pressure and in almost every case 60–62 grams of ethoxymethylenemalonic ester were obtained. Sixty-two grams of ethoxymethylenemalonic ester is only 45.9 per cent of the calculated. However, this yield is in perfect agreement with Claisen's statement that 500 grams of malonic ester, in five portions, gave 307 grams of distilled ethoxymethylenemalonic ester. The amount of ethyl acetate obtained indicated that at least 81 grams of ethoxymethylenemalonic ester was formed from 100 grams of malonic ester.

We have now found that it is not necessary or even advisable, on account of loss, to prepare pure distilled ethoxymethylenemalonic ester for the present condensation. In fact, a much better yield of condensation product is obtained if the oil is not distilled.

¹ Ann. Chem. (Liebig), **297**, 75 (1897).

Preparation of the Potassium Salt of 2-Ethylmercapto-5-carb-

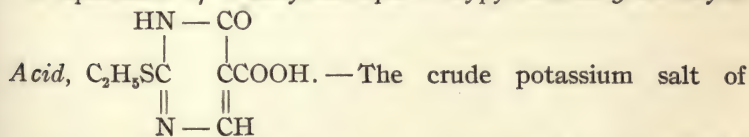


ment, after heating the above mixture at ordinary pressure for three hours, distilling the ethyl acetate as stated, and filtering from zinc chloride, everything was then removed that distilled below 117° at about 20 mm. pressure. The residue in this case weighed 105 grams. This was added to 100 grams of the addition product of ethyl bromide and thio-urea dissolved in 100 cc. of water. To this cold solution 60 grams of potassium hydroxide in 120 cc. of water were slowly added and the mixture was not allowed to warm. The solution soon became semisolid from the separation of the potassium salt. It was found that more separated on standing. The mixture was allowed to stand for two days at ordinary temperature. The salt which separated then, on filtering and drying, weighed 113 grams, or nearly twice as much crude salt as was obtained from 100 grams malonic ester in our previous work.

In another experiment everything was removed that distilled below 120° at 25 mm. pressure. The remaining oil weighed 100 grams. When this was condensed with 2-ethylpseudo-thiourea as above, the weight of the potassium salt, after washing with a little alcohol, was 91 grams.

The above yields, of course, do not represent the weights of pure substances, they merely serve to give a general idea. We conclude, however, that the above process yields almost 75 per cent of the calculated of ethoxymethylenemalonic ester; 105 grams is 77.7 per cent of the calculated.

Preparation of 2-Ethylmercapto-6-oxypyrimidine-5-carboxylic



2-ethylmercapto-5-carbethoxy-6-oxypyrimidine was saponified

by warming with potassium hydroxide. For about 27–30 grams of this salt 15 grams of potassium hydroxide were used. If a smaller proportion of alkali was used the saponification was liable to be less smooth.

The potassium salt was dissolved in alcohol, the alkali in water added, and the solution evaporated to dryness on the steam bath. The residue was taken up in water and evaporated again, when the saponification was usually found to be complete. The acid was then precipitated from the filtered aqueous solution of this residue by means of hydrochloric acid. It separated in an almost pure condition as shown by its melting point (near 167°). Care must be taken not to add too much hydrochloric acid since the mercapto acid is soluble in a certain excess. On the other hand, if the solution is not made distinctly acid, the potassium salt of 2-ethylmercapto-6-oxypyrimidine-5-carboxylic acid is obtained. This melts with effervescence above 250°. If the precipitate melts near 131° the saponification is not complete.

Twenty-seven grams of the washed potassium salt gave 17 grams of 2-ethylmercapto-6-oxypyrimidine-5-carboxylic acid. The same quantity of salt in another experiment gave 18 grams of acid. This is 88.6 per cent of the calculated.

The Acid Chloride of 2-Ethylmercapto-6-chlorpyrimidine-5-carboxylic Acid, $\text{C}_2\text{H}_5\text{SC}$ $\begin{array}{c} \text{N}=\text{CCl} \\ | \\ \text{CCOCl} \\ || \\ \text{N}-\text{CH} \end{array}$.—The best yield of this

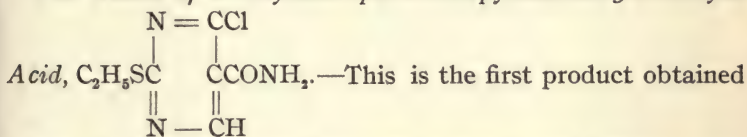
compound was obtained when perfectly dry 2-ethylmercapto-oxypyrimidine-5-carboxylic acid and phosphorus oxychloride were mixed in the proportion of 5 cc. of the chloride to 1 gram of the acid and then heated, with a return condenser, in an oil bath. The temperature of the bath was kept at 130°–150° or so that the solution boiled quietly and until hydrogen chloride was no longer evolved. This required from 2 to 3 hours, although solution took place soon after heating. Most of the phosphorus oxychloride was then removed under reduced pressure at 100° and the residue, a thick oil, was poured upon

cracked ice. It then changed to a granular solid. The yield of crude chloride was 85 per cent of the calculated. To prepare the amide of 2-ethylmercapto-6-aminopyrimidine-5-carboxylic acid, instead of pouring on ice, it is poured directly into concentrated ammonia (see below). The yield of crude amide is then almost quantitative. In another experiment 18 grams of the acid and 45 cc. of phosphorus oxychloride were boiled on a sand bath. Under these conditions the material was completely decomposed. The yield of this chloride may vary decidedly under slight changes of conditions.

This acid chloride was very soluble in cold benzene, ether, and ligroin. It was purified for analysis by dissolving in ligroin and evaporating at the temperature of the room. Radiating clusters of colorless prisms were formed, which melted to a clear oil at 38°-40°. Analysis:

	Calculated for $C_7H_6ON_2Cl_2S$.	Found.
N	11.81	11.76

The Amide of 2-Ethylmercapto-6-chlorpyrimidine-5-carboxylic



by the action of aqueous ammonia on the above acid chloride. When the acid chloride was added to cold concentrated aqueous ammonia, an immediate reaction took place with the liberation of heat and a white powder was formed. This was washed with water to remove ammonium chloride. When dried it was found to be moderately soluble in hot alcohol, benzene, and toluene, and difficultly soluble in boiling ether. It crystallized from benzene in long, hairlike crystals which formed a fibrous mat. It then melted sharply to a colorless oil at 134° and the yield was almost quantitative. Analysis:

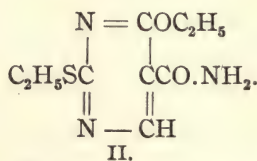
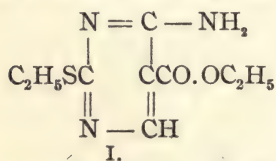
	Calculated for $C_7H_8ON_2ClS$.	I.	Found.	II.
N	19.31	19.36		19.24

When this chloramido compound was first obtained it became a question which chlorine atom had been replaced in the above

acid chloride. In order to decide this point, two grams of the chloramido compound were dissolved in absolute alcohol and added to a solution of 0.25 gram of sodium, also in alcohol. An immediate precipitate resulted and heat was liberated. On cooling, a mass of well defined prisms separated. The sodium chloride was removed by washing with water. The residue was then found to be insoluble in hot water but it crystallized from alcohol, in which it was moderately soluble. The substance melted at 134° , the same temperature as the chloramido compound. However, it was free from chlorine and when mixed with the chloramido compound the melting point of the mixture was lowered about 30° . The yield and nitrogen determinations agreed with the calculated for an ethoxy derivative.

	Calculated for $C_9H_{13}O_2N_3S$.	I.	Found.	II.
N	18.50	18.54	—	18.45

This ethoxy derivative should have the structure represented by one of the following formulas:



The first of these two compounds has already been described by us in our twenty-sixth paper, p. 597. It melts at 102° . To the ethoxy compound now obtained, melting at 134° , is therefore assigned the structure represented by formula II. It follows that the chloride from which it was prepared has the chlorine atom in the 6 position and is the amide of 2-ethyl-mercapto-6-chlorpyrimidine-5-carboxylic acid.

The Amide of 2-Ethylmercapto-6-aminopyrimidine-5-carboxylic

$$\begin{array}{c}
 \text{N} = \text{C} - \text{NH}_2 \\
 | \qquad \qquad | \\
 \text{C}_2\text{H}_5\text{SC} \quad \text{CCONH}_2 \\
 || \qquad \qquad || \\
 \text{N} - \text{CH}
 \end{array}$$
 Acid, —If the acid chloride of 2-ethyl-mercapto-6-chlorpyrimidine-5-carboxylic acid is warmed with

concentrated ammonia both chlorine atoms are replaced by the amino group and the amide of 2-ethylmercapto-6-amino-pyrimidine-5-carboxylic acid is formed. We have prepared this compound by slowly adding the acid chloride (it reacts vigorously) to a considerable excess of aqueous ammonia in an evaporating dish and then warming on the steam bath. Not very much of the aminoamide thus formed dissolves in the hot ammonia nor is it soluble to any great extent in boiling water. It should be warmed until the insoluble material melts above 200° . When purified by crystallizing from alcohol, in which it is moderately soluble, it separates in rectangular crystals, little stout prisms which separate slowly and melt to an oil at 218° – 219° . It is soluble in glacial acetic acid but insoluble in alkali. The yield of crude product melting at 214° is almost quantitative. Thirteen grams of mercapto acid gave 12 grams of this amide. Analysis:

	Calculated for $C_7H_{10}ON_4S$.	I.	Found. II.
N	28.28	27.99	27.91

Action of Hydrochloric Acid.—When this amide is digested on the steam bath with concentrated hydrochloric acid ethyl mercaptan is evolved and the amido group attached to the carboxyl radical in position 5 is removed. If the resulting solution is allowed to cool slowly the *hydrochloride of cytosine-5-carboxylic acid* separates in the form of large prisms which contain one molecule of water and melt sharply at 276° to a brown oil and with some effervescence. This salt was identified by its properties previously described and by the following analyses:

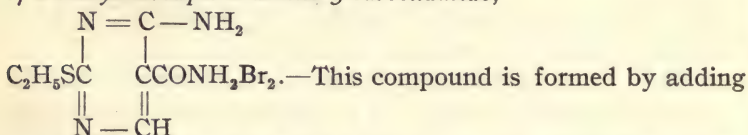
	Calculated for $C_5H_5O_3N_3.HCl.H_2O$.	Found.
H_2O	8.59	8.75

The water determination was made by heating the substance at 120° – 130° . A nitrogen determination then gave the following results:

	Calculated for $C_5H_5O_3N_3.HCl$.	Found.
N	21.92	22.21

Prolonged digestion of the aminoamide with dilute hydrochloric acid or potassium hydroxide also removed the amido group from the 5 position. For a description of the less energetic action of hydrochloric acid on this amide see under cytosine-5-carboxamide. It did not dissolve in a solution of potassium hypobromite (16 grams of bromine in 280 cc. of 10 per cent alkali).

The Action of Dry Bromine: The Dibrom Addition Product of 2-Ethylmercapto-6-amino-5-carboxamide,



the amide directly to liquid bromine. They unite with evolution of considerable heat. Eight grams of finely powdered and carefully dried amide were added in small portions, best through a sieve to prevent the formation of lumps, to about 15 cc. of dry bromine. The amide then dissolved at once in the bromine. When all of the amide had been added the excess of bromine was allowed to evaporate at the temperature of the room. This treatment left a yellow, crystalline crust that was powdered in a mortar in order to liberate the inclosed bromine. The yield at this point was quantitative if care was taken to exclude moisture; otherwise some decomposition took place. Analyses of the air-dried material gave the following results:

	Calculated for $\text{C}_7\text{H}_{10}\text{ON}_4\text{Br}_2\text{S}$.	I.	Found. II.
N	15.64	15.50	15.91

When the dibrom addition product was warmed with water unaltered amide was obtained.

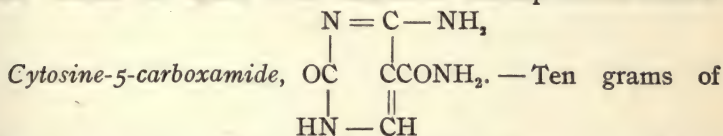
Action of Alkali.—The unaltered amide was also obtained when this material was treated with alkali. One gram of the addition product was added to 10 cc. of water containing 1 gram of potassium hydroxide. Only a small portion dissolved even after heating on the steam bath. On filtering and acidifying the filtrate with acetic acid a very small amount of material not soluble in ammonia was precipitated. This had all the

properties of cytosine-5-carboxamide. Its hydrochloric acid solution gave a precipitate with nitric acid.

Behavior on Heating.—When the dibrom addition product was heated at 120°–135° a point was finally reached where the evolution of hydrogen bromide seemed to stop or proceed more slowly. The brownish white material then agreed in weight with the loss of about one molecular proportion of hydrogen bromide. There was a loss from 13.5 grams of the addition product of 3.3 grams while the calculated loss is 3.1 grams. Nitrogen determinations gave the following results:

	Calculated for $C_7H_9ON_4BrS$.	I.	Found. II.
N	20.21	20.47	20.76

This product had an odor similar to that of the sulphur chlorides. It dissolved only partially in hot water, alcohol, ethyl acetate, or amyl acetate, and it behaved like a mixture of more or less decomposed material. It dissolved partially in a solution of sulphur dioxide, and ammonia then precipitated unaltered mercaptoaminoamide. This might result from the hydrobromic acid salt of the amide possibly contained in the mixture, or from unaltered dibrom addition product. A solvent suitable to isolate a monobromamide, if formed here, was not found, and the results obtained on treating the material with alkali would suggest that in spite of the analyses such a compound was not formed. Sometimes the product would dissolve completely in alkali. When dark in color it usually left undissolved amorphous, dark colored decomposition products mixed at times with unaltered mercaptoaminoamide.



the brom product obtained by heating the above dibrom addition product of the amide of 2-ethylmercapto-6-amino-pyrimidine-5-carboxylic acid were dissolved in 50 cc. of water containing 10 grams of potassium hydroxide. In this particular experiment complete solution resulted. On acidifying with

acetic acid mercaptan was evolved and a granular precipitate was obtained. This was filtered and dissolved in hot water to which a little hydrochloric acid was added. The hot solution was then made strongly alkaline with ammonia which reprecipitated the base. This treatment removed any cytosine-5-carboxylic acid that was present, the acid being soluble in ammonia. The best yield of aminoamide obtained at this point was about 75 per cent of the theory. It varied considerably. For analysis the aminoamide was purified by recrystallizing from dilute hydrochloric acid. The hydrochloride was then dissolved in water, with the aid of a little hydrochloric acid, and the base reprecipitated with ammonia, washed thoroughly with water and alcohol, and finally dried over calcium chloride. It did not lose water when heated at 120° – 130° (Analyses I. II. and III.).

When we first obtained this material attempts were made to determine nitrogen by Kjeldahl's method and it was found that neither the free base nor any of its salts that we tried gave results agreeing with the calculated. The figures invariably came several per cent too low. It appears probable that the failure to obtain correct results by Kjeldahl's method was due to the fact that the weakly basic properties of the compound permitted the escape of material on heating the sulphuric acid solution. This might have escaped unnoticed if we had no theory to check the results.

I. 0.0763 gram of substance gave 24.6 cc. of nitrogen at 22° and 770 mm. pressure.

II. 0.2462 gram of substance gave 0.0877 gram of H_2O and 0.3575 gram of CO_2 .

III. 0.1440 gram of substance gave 0.0526 gram of H_2O and 0.2093 gram of CO_2 .

	Calculated for $C_5H_6O_2N_4$.	I.	II.	Found.	III.	IV.
C	38.96	39.60	39.58			
H	3.89	4.00	3.90			
N	36.36				37.00	36.38

Cytosine-5-carboxamide was also obtained by the action of concentrated hydrochloric acid on 2-ethylmercapto-6-amino-

pyrimidine-5-carboxamide. One gram of the mercapto-aminoamide was evaporated to dryness with 15 cc. of concentrated hydrochloric acid on the steam bath. The residue was made strongly alkaline with ammonia. This extracted cytosine-5-carboxylic acid and left a mixture which was boiled with alcohol. Unaltered mercaptoaminoamide dissolved. The insoluble material was purified by dissolving in dilute hydrochloric acid and precipitating with an excess of ammonia while the solution was hot. This gave very small, microscopic, lenticular crystals that did not show signs of melting at 310° . When a drop of nitric acid was added to the hydrochloric acid solution a precipitate of the nitrate was formed. (Analysis IV.).

Cytosine-5-carboxamide is almost insoluble in water and the ordinary organic solvents. It dissolves readily in cold alkalies, but it is almost insoluble in ammonia. It does not dissolve in acetic acid. It dissolves in dilute mineral acids and yields beautiful crystalline salts which are dissociated by water. The aminoamide is a weak base. Its solubility in alkali is in accordance with the presence of —NH—CO— groups. The free aminoamide prepared from the brom derivative, when obtained by precipitating from alkaline solution by acetic acid or from the hydrochloric acid solution with ammonia, usually appears to be an amorphous powder. Before purifying it has a more or less brownish color. Its method of separation along the lines of stirring indicates a crystallization but the crystals are too minute to be determined under the microscope.

Action of Concentrated Hydrochloric Acid on Cytosine-5-carboxamide: Cytosine-5-carboxylic Acid.—The amide obtained from the bromamide (0.6 gram) was boiled with 50 cc. of concentrated hydrochloric acid for about five minutes and the resulting solution evaporated to dryness on the steam bath. The residue dissolved completely in ammonia. On acidifying with acetic acid a precipitate of cytosine-5-carboxylic acid was obtained. This decomposed at 256° . Analysis:

	Calculated for $\text{C}_5\text{H}_5\text{O}_3\text{N}_3$.	Found.
N	27.09	27.53

This acid was described in a previous paper. It should be added that, like the amide, it is almost insoluble in water and alcohol. It was obtained in an amorphous condition. When precipitated from its solution in ammonia by acetic acid it separates as a gelatinous precipitate which is difficult to filter. It is better to obtain the acid by evaporating the ammonia solution. It then separates as a finely divided powder which is readily filtered. It is also readily identified by its decomposing point, 256° , and its crystalline hydrochloride which contains 1 molecule of water of crystallization.

Cytosine-5-carboxamide Hydrochloride, $C_5H_6O_2N_4.HCl$.—The base dissolved in moderate quantities in hot dilute hydrochloric acid. On cooling, the hydrochloride separated almost completely in clusters of colorless, stout, pointed prisms which did not have a definite melting point. They did not lose weight on heating at 110° , when dried over calcium chloride. When heated at 140° – 150° they lost their lustre, hydrochloric acid being slowly given off. The salt was dried at 110° for analysis:

I. 0.0739 gram of substance gave 19.0 cc. of N at 22° and 768 mm.

II. 0.0791 gram of substance gave 0.0607 gram of $AgCl$.

	Calculated for $C_5H_6O_2N_4.HCl$.	I.	Found.	II.
N	29.40	29.42		
Cl	18.64			18.97

Cytosine-5-carboxamide Nitrate, $C_5H_6O_2N_4.HNO_3$.—This is the most difficultly soluble and characteristic salt. It is formed not only by dissolving the amide in hot nitric acid but also on adding nitric acid to solutions of other salts of the base.

Cytosine-5-carboxamide dissolved very slightly in hot nitric acid. On cooling, the nitrate separated in beautiful truncated octahedrons. When nitric acid was added to a solution of the base in dilute hydrochloric acid an immediate crystalline precipitate of the nitrate came down. It then formed tufts of short hairs, which did not decompose at 300° , although they sublimed slowly below that temperature. They did not lose weight on heating at 115° . Analysis:

	Calculated for $C_5H_6O_2N_4.HNO_3$.	Found.
N	32.26	32.05

Cytosine-5-carboxamide Sulphate, $(C_5H_6O_2N_4)_2H_2SO_4$.—A solution of the amide was made in hot water containing about 10 per cent sulphuric acid. The sulphate separated, on cooling, in scales with a pearly lustre. They did not melt at 300° and no loss in weight took place on heating at 110° . Analysis:

0.0653 gram of substance gave 0.0386 gram $BaSO_4$.

	Calculated for $(C_5H_6O_2N_4)_2H_2SO_4$.	Found.
S	7.88	8.11

Cytosine-5-carboxamide Picrate, $C_5H_6O_2N_4.C_6H_2(NO_2)_3OH$.—The amide was dissolved in hot water to which a few drops of hydrochloric acid had been added. On adding an aqueous solution of picric acid an immediate precipitate was formed. This crystallized from an aqueous solution of picric acid. It dissociates in water into small, yellow prisms that began to decompose at about 260° – 270° . The salt was found to be anhydrous.

I. 0.0531 gram of substance gave 11.6 cc. of N at 20° and 771 mm.

II. 0.0967 gram of substance gave 21.2 cc. of N at 18° and 771 mm.

	Calculated for $C_{11}H_9O_9N_7$.	I.	Found.	II.
N	25.59	25.34		25.64

The papers on pyrimidines which have been published from this laboratory, under the direction of Dr. Treat B. Johnson and the writer, have appeared in two journals. Some of these papers have not been numbered and one has received an incorrect number, there being two twenty-first papers. For the sake of reference a complete list of these papers up to the end of the year 1907 is now given. The papers are arranged and numbered in the order in which they appeared. The numbers correspond with those already given in the literature, with the exception of the paper which has been incorrectly numbered. By referring to this paper as the twenty-

fourth the order then remains otherwise undisturbed. The following is a complete list up to the end of the year 1907.

1. Researches on the Cycloamidines: Pyrimidine Derivatives. H. L. Wheeler: *THIS JOURNAL*, 20, 481 (1898).
2. On Some Condensation Products of the Pseudothiourcas: Synthesis of Uracil, Thymine, and Similar Compounds. Henry L. Wheeler and Henry F. Merriam: *THIS JOURNAL*, 29, 478 (1903).
3. Syntheses of Aminooxypyrimidines having the Composition of Cytosine: 2-Amino-6-oxypyrimidine and 2-Oxy-6-aminopyrimidine. Henry L. Wheeler and Treat B. Johnson: *THIS JOURNAL*, 29, 492 (1903).
4. On Cytosine or 2-Oxy-6-aminopyrimidine from Triticonucleic Acid. Henry L. Wheeler and Treat B. Johnson: *THIS JOURNAL*, 29, 505 (1903).
5. 5-Methylcytosine. Henry L. Wheeler and Treat B. Johnson: *THIS JOURNAL*, 31, 591 (1904).
6. Synthesis of 2-Amino-5-methyl-6-oxypyrimidine. Treat B. Johnson and Samuel H. Clapp: *THIS JOURNAL*, 32, 130 (1904).
7. 2-Oxy-4,6-diaminopyrimidine. Henry L. Wheeler and George S. Jamieson: *THIS JOURNAL*, 32, 342 (1904).
8. The Structure of Some Substitution Products. Henry L. Wheeler and H. Stanley Bristol: *THIS JOURNAL*, 33, 437 (1905).
9. The Action of Potassium Thiocyanate upon Some Imidechlorides. Henry L. Wheeler and H. Stanley Bristol: *THIS JOURNAL*, 33, 448 (1905).
10. The Action of Aqueous and Alcoholic Ammonia and Aniline on Some Halogen- and Mercaptopyrimidines. Treat B. Johnson and Carl O. Johns: *THIS JOURNAL*, 34, 176 (1905).
11. 2-Ethylmercapto-5-amino-6-oxypyrimidine. Treat B. Johnson: *THIS JOURNAL*, 34, 191 (1905).
12. 2,5-Diamino-6-oxypyrimidine. Treat B. Johnson and Carl O. Johns: *THIS JOURNAL*, 34, 554 (1905).
13. Some Iodopyrimidines: 5-Iodocytosine. Treat B. Johnson and Carl O. Johns: *J. Biol. Chem.*, 1, 305 (1906).
14. On Methods of Synthesizing Isobarbituric Acid and 5-Oxycytosine. Treat B. Johnson and Elmer V. McCollum: *J. Biol. Chem.*, 1, 437 (1906).
15. The Action of Potassium Thiocyanate upon Imidechlorides. Treat B. Johnson and Elmer V. McCollum: *THIS JOURNAL*, 36, 136 (1906).
16. The Formation of Purines from Ureaprimidines. Treat B. Johnson and Elmer V. McCollum: *THIS JOURNAL*, 36, 149 (1906).
17. 5-Nitrocytosine and its Reduction to 2-Oxy-5,6-diaminopyrimidine. Treat B. Johnson, Carl O. Johns, and Frederick W. Heyl: *THIS JOURNAL*, 36, 160 (1906).
18. 5-Ethylcytosine. Treat B. Johnson and George A. Menge: *J. Biol. Chem.*, 2, 105 (1906).
19. Synthesis of Uracil-5-carboxylic Acid. Henry L. Wheeler, Treat B. Johnson, and Carl O. Johns: *THIS JOURNAL*, 37, 392 (1907).
20. Some Condensation Products of a Substituted Pseudothiourca:

Synthesis of 1-Methyluracil. Treat B. Johnson and F. W. Heyl: *THIS JOURNAL*, **37**, 628 (1907).

21. On a Color Test for Uracil and Cytosine. Henry L. Wheeler and Treat B. Johnson: *J. Biol. Chem.*, **3**, 183 (1907).

22. On Some Salts of Cytosine, Isocytosine, 6-Aminopyrimidine, and 6-Oxypyrimidine. Henry L. Wheeler: *J. Biol. Chem.*, **3**, 285 (1907).

23. Uracil-4-carboxylic Acid. Henry L. Wheeler: *THIS JOURNAL*, **38**, 358 (1907).

24. The Action of Methyl Iodide on 2-Anilino-6-oxypyrimidine and the Synthesis of 2-Anilinopyrimidine. Treat B. Johnson and Frederick W. Heyl: *THIS JOURNAL*, **38**, 237 (1907).

25. Synthesis of Thymine-4-carboxylic Acid. Treat B. Johnson: *J. Biol. Chem.*, **3**, 299 (1907).

26. Synthesis of Cytosine-5-carboxylic Acid. Henry L. Wheeler and Carl O. Johns: *THIS JOURNAL*, **38**, 594 (1907).

27. Synthesis of Thymine-5'-carboxylic Acid. (Uracil-5-acetic Acid). Treat B. Johnson and Carl Frank Speh: *THIS JOURNAL*, **38**, 602 (1907).

28. Synthesis of 4-Methyluracil-5-acetic Acid. Treat B. Johnson and Frederick W. Heyl: *THIS JOURNAL*, **38**, 659 (1907).

NEW HAVEN, CONN.,
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CLX.—RESEARCHES ON PYRIMIDINES:
SYNTHESIS OF 4-METHYLCYTOSINE.

[THIRTY-SEVENTH PAPER].

By CARL O. JOHNS.

There are two methyl derivatives of cytosine having the methyl group attached to carbon. Of these, 5-methylcytosine (Formula I.) has been described in the fifth paper of

this series,¹ while a description of the synthesis and properties of 4-methylcytosine (V.) will be given in the following pages.

Acetoacetic ester condenses readily in an aqueous solution of sodium hydroxide with pseudoethylthiourea hydrobromide to give an excellent yield of 2-ethylmercapto-4-methyl-6-oxypyrimidine (II.). This compound has been prepared by List² but his method requires several days, and, calculating from the weight of acetoacetic ester used, the yields are only about one-half as great as those obtained by the method here described.

When 2-ethylmercapto-4-methyl-6-oxypyrimidine is boiled with phosphorus oxychloride it yields 2-ethylmercapto-4-methyl-6-chlorpyrimidine (III.). When heated in a sealed tube at 140°–150° with alcoholic ammonia the chlorine in this compound is replaced by an amino group and 2-ethylmercapto-4-methyl-6-aminopyrimidine (IV.) is obtained. This is readily converted into 4-methylcytosine (V.) by digesting with concentrated hydrochloric acid and precipitating the base with a slight excess of ammonium hydroxide.

The chloride (III.) reacts more readily with alcoholic sodium ethylate than it does with alcoholic ammonia. Action takes place at room temperature. Sodium chloride separates and 2-ethylmercapto-4-methyl-6-ethoxypyrimidine (VI.) is formed.

4-Methylcytosine can easily be distinguished from 5-methylcytosine. It does not melt at 310°, while 5-methylcytosine melts with effervescence at 270°. It is far less soluble in water than is 5-methylcytosine. Moreover, 4-methylcytosine crystallizes from water in long, anhydrous prisms, while 5-methylcytosine gives flat prisms containing one-half molecule of water.

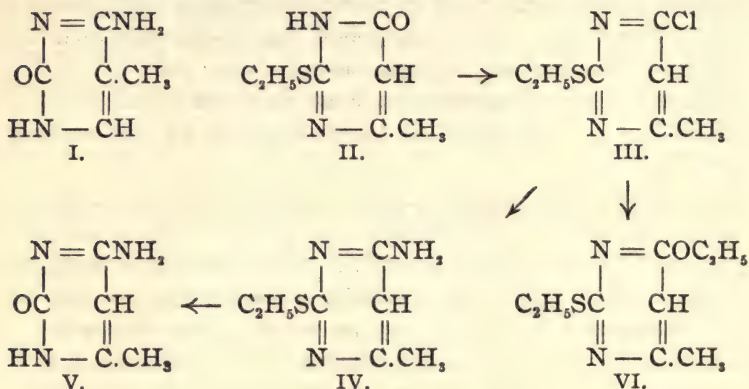
4-Methylcytosine gives a very characteristic basic hydrochloride containing 3 molecules of base to 1 molecule of hydrogen chloride while 5-methylcytosine under similar conditions gives a hydrochloride containing 2 molecules of base to one of acid.

¹ Wheeler and Johnson: *THIS JOURNAL*, **31**, 591 (1904).

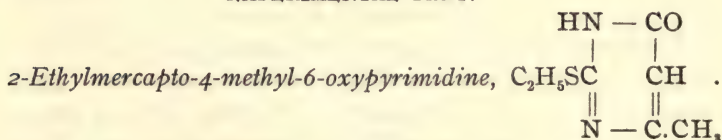
² *Ann. Chem. (Liebig)*, **236**, 14 (1886).

When crystallized from concentrated solutions of the common acids, 4-methylcytosine gives a series of normal salts.

4-Methylcytosine has been used for the preparation of some purine derivatives to be described in another paper.



EXPERIMENTAL PART.



—List¹ prepared this compound by heating 2-thio-4-methyl-6-oxypyrimidine with ethyl iodide in the presence of sodium ethylate. It can be obtained more easily and in better yields by condensing pseudoethylthiourea hydrobromide with acetoacetic ester in an aqueous solution of sodium hydroxide. This condensation is very smooth and the yields range from 80 to 90 per cent of the theoretical quantity.

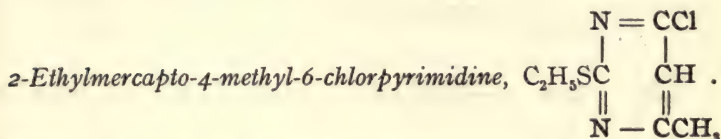
Ninety-three grams of pseudoethylthiourea hydrobromide are dissolved in 100 cc. of water and this solution is mixed with 65 grams of acetoacetic ester. To this mixture is slowly added a solution of 40 grams of sodium hydroxide in 80 cc. of water. Condensation takes place at once, but to insure complete reaction the mixture is allowed to stand at room temperature overnight. When the resulting clear solution

¹ Ann. Chem. (Liebig), **236**, 14 (1886).

is acidified with acetic acid about 75 grams of 2-ethylmercapto-4-methyl-6-oxypyrimidine are obtained. When crystallized from dilute alcohol it melts at 144° – 145° and possesses all the properties of List's compound.

Analyses (Kjeldahl):

	Calculated for $C_7H_{10}ON_2S$.	I.	Found.	II.
N	16.47	16.49		16.52

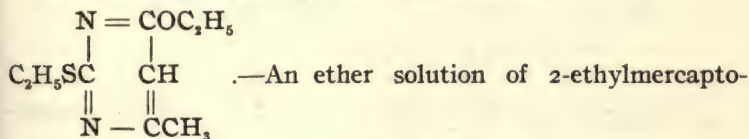


—Twenty grams of 2-ethylmercapto-4-methyl-6-oxypyrimidine were heated with 60 cc. of phosphorus oxychloride in an oil bath kept at 130° – 135° until hydrogen chloride was no longer evolved. The excess of phosphorus oxychloride was removed under diminished pressure and the resulting thick oil was poured on cracked ice. The chloride was extracted with ether and dried over calcium chloride. When the ether was evaporated a clear, red oil remained. This boiled at 142° at 15 mm. pressure. The yield of pure chloride was about 75 per cent of the calculated quantity. This chloride is very stable towards water and alcohol.

Analyses (Kjeldahl):

	Calculated for $C_7H_9N_2SCl$.	I.	Found.	II.
N	14.85	14.71		15.09

2-Ethylmercapto-4-methyl-6-ethoxypyrimidine,



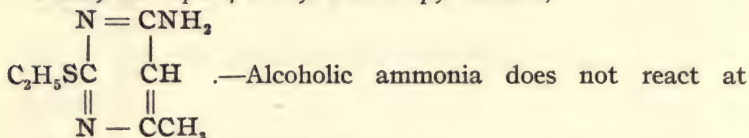
4-methyl-6-chlorpyrimidine was added to alcohol containing an excess of sodium, calculating from the chloride. An immediate reaction took place with the liberation of heat.

The excess of alcohol was evaporated, and, after adding water, the oil was shaken out with ether and dried over calcium chloride. When the ether was evaporated an oil remained. This boiled at 154° at 20 mm. pressure.

Analyses (Kjeldahl):

	Calculated for $C_9H_{14}ON_2S$.	I.	Found. II.
N	14.14	14.08	14.43

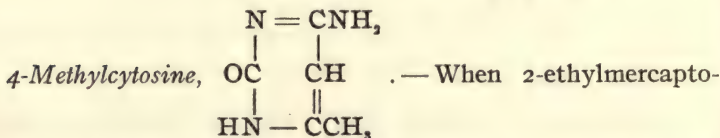
2-Ethylmercapto-4-methyl-6-aminopyrimidine,



room temperature with 2-ethylmercapto-4-methyl-6-chloropyrimidine. Sixteen grams of the chloride were heated in a sealed tube for 4 hours at 140° – 150° with about 75 cc. of alcoholic ammonia saturated at 0° . The tube, when cooled, was lined with ammonium chloride and crystals of the new amino compound. The reaction was very smooth and the alcohol remained colorless. After evaporating to dryness, the residue was washed with cold water and recrystallized from dilute alcohol. The crystals melted at 115° – 116° to a clear oil. They have a tetrahedral outline and show a great tendency to twin. They are easily soluble in cold alcohol and acetic acid, moderately soluble in cold benzene, and difficultly soluble in boiling water.

Analyses (Kjeldahl):

	Calculated for $C_7H_{11}N_3S$.	I.	Found. II.
N	24.85	24.83	25.07



4-methyl-6-aminopyrimidine is evaporated with concentrated hydrochloric acid ethyl mercaptan is evolved and an almost

theoretical yield of 4-methylcytosine monohydrochloride is obtained. The base is obtained from this salt by adding an excess of ammonium hydroxide. 4-Methylcytosine crystallizes from water in anhydrous, slender, brittle prisms. These crystals do not melt at 310° , but decompose slowly without effervescence at higher temperatures. 4-Methylcytosine is moderately soluble in boiling water. At 24° , 0.36 gram is dissolved by 100 cc. of water. It is soluble in cold aqueous ammonia and in cold acetic acid.

Analyses (Kjeldahl):

	Calculated for $C_5H_7ON_3$.	I.	Found. II.
N	33.60	33.52	33.39

4-Methylcytosine Monohydrochloride, $C_5H_7ON_3.HCl$.—This salt is obtained when 2-ethylmercapto-4-methyl-6-aminopyrimidine is digested with concentrated hydrochloric acid. It is also formed by crystallizing 4-methylcytosine from 20 per cent hydrochloric acid. It is moderately soluble in hot hydrochloric acid and separates on cooling in blunt, flat prisms with a hexagonal appearance. When dried over potassium hydroxide it does not lose water at 110° . In a capillary tube it begins to shrivel at about 280° and decomposes slowly above 300° .

Analyses:

	Calculated for $C_5H_7ON_3.HCl$.	I.	Found. II.
N	26.00	26.10	26.09
Cl	21.98	21.81	

The anhydrous monohydrochloride of 4-methylcytosine is also obtained unaltered when its aqueous solution is saturated with hydrogen chloride and evaporated in a desiccator. The crystals thus obtained did not lose weight at 125° .

Analysis:

	Calculated for $C_5H_7ON_3.HCl$.	Found.
Cl	21.98	21.95

4-Methylcytosine Basic Hydrochloride, $(C_5H_7ON_3)_3.HCl$.—Such a salt was formed when a hot aqueous solution of 0.25

gram of the base was mixed with an aqueous solution of 0.32 gram of the monohydrochloride. The basic salt separated in scales with a pearly lustre. These began to shrivel at about 270° and turned brown above 280° but did not melt at 310° . These crystals lost weight when dried at 130° – 140° , but attempts to determine water of crystallization gave results that differed widely, but indicated that one molecule of water was probably present. The dried salt contained 3 molecules of the base and 1 molecule of hydrogen chloride. This same salt was obtained when equal weights of the base and monohydrochloride were recrystallized from water.

Analyses of the dried salt:

	Calculated for (C ₅ H ₇ ON ₃) ₃ .HCl.	I.	Found. II.	III.
N	30.61		30.26	
Cl	8.62	8.51		8.49

4-Methylcytosine Nitrate, C₅H₇ON₃.HNO₃.—One-half gram of 4-methylcytosine was crystallized from 10 cc. of 25 per cent nitric acid. The salt separated in round clusters of blunt prisms. It did not contain water of crystallization.

0.0983 gram of substance gave 25.2 cc. of moist nitrogen at 18° and 770 mm. pressure.

	Calculated for C ₅ H ₇ ON ₃ .HNO ₃ .	Found.
N	29.79	29.94

4-Methylcytosine Sulphate, (C₅H₇ON₃)₂.H₂SO₄.H₂O.—When 4-methylcytosine was crystallized from 25 per cent sulphuric acid, two molecules of the base united with one molecule of sulphuric acid to form a normal sulphate containing one molecule of water of crystallization. The crystals were large, flat prisms that did not lose water at 110° , but lost one molecule of water slowly at 160° – 170° .

Analyses:

	Calculated for (C ₅ H ₇ ON ₃) ₂ .H ₂ SO ₄ .H ₂ O.	I.	Found. II.	III.
H ₂ O	4.91		4.83	
N	22.95	22.79		22.82
S	8.74		8.88	

4-Methylcytosine Picrate, $C_5H_7ON_3 \cdot C_6H_2(NO_2)_3OH$.—When an aqueous solution of picric acid is added to a solution of 4-methylcytosine, an immediate precipitate is obtained. This picrate is difficultly soluble in hot water and crystallizes in beautiful, yellow needles that turn brown at about 265° and decompose slowly above that temperature.

0.0858 gram of substance gave 17.3 cc. of moist nitrogen at 18° and 772 mm. pressure.

N	Calculated for	Found.
	$C_5H_7ON_3 \cdot C_6H_2(NO_2)_3OH$.	
	23.73	23.65

NEW HAVEN, CONN.,
May, 1908.

[Reprinted from the American Chemical Journal, Vol. XL.
No. 5. November, 1908.]

[Contributions from the Sheffield Laboratory of Yale University.]

CLXI.—RESEARCHES ON PYRIMIDINES:
SYNTHESES OF SOME BENZYL DERIVATIVES
OF URACIL AND THYMINE.

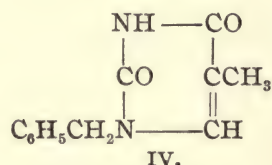
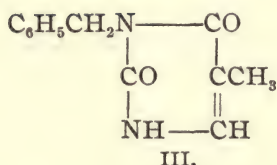
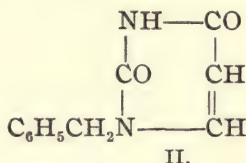
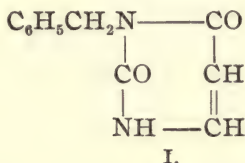
[THIRTY-EIGHTH PAPER.]

BY TREAT B. JOHNSON AND JOHN H. DERBY, JR.

In order to determine the structure of some new nitrogen derivatives of uracil and thymine it was essential to have knowledge of some characteristic nitrogen-alkyl derivatives of

these pyrimidines of known constitution. The only nitrogen-alkyl derivatives of uracil and thymine mentioned in the literature are 1,3-dimethylthymine¹ and the methyl and ethyl compounds, which have been described in previous papers from this laboratory.² These alkyl pyrimidines were not suitable for our work on account of their solubility, and difficulty of isolation when accompanied by impurities. Furthermore, 3-methyluracil has not been synthesized.

With the anticipation that the nitrogen-benzyl derivatives of uracil and thymine might be found to be more insoluble, and suitable for our work, we undertook this investigation. We shall describe in this paper the methods of preparation and the properties of 1-benzyluracil, I., 3-benzyluracil, II., 1-benzylthymine, III., and 3-benzylthymine, IV.



Johnson and Heyl³ showed that methyl iodide reacts with 2-ethylmercapto-6-oxypyrimidine,⁴ in presence of alkali, giving 1-methyl-2-ethylmercapto-6-oxypyrimidine, V. They did not observe the formation of the isomeric 2-ethylmercapto-3-methyl-6-oxypyrimidine, VI. Wheeler and Liddle⁵ observed, on the other hand, that ethyl chloracetate reacts with this mercaptopyrimidine, giving 2-ethylmercapto-3-ethylacetate-6-

¹ Steudel: *Z. physiol. Chem.*, **30**, 539.

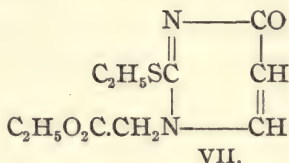
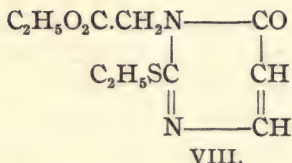
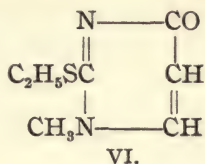
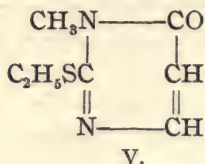
² Johnson and Heyl: *THIS JOURNAL*, **37**, 628; Johnson and Clapp: *J. Biol. Chem.* **5**, 49.

³ *Loc. cit.*

⁴ *THIS JOURNAL*, **29**, 478, 492.

⁵ *J. Am. Chem. Soc.*, **30**, 1152.

oxypyrimidine, VII., instead of the isomeric mercaptopyrimidine, VIII.



We now find that benzyl chloride reacts with 2-ethylmercapto-6-oxypyrimidine in presence of alkali, giving a mixture of two isomeric mercaptopyrimidines melting at 77° and 139° . They were converted quantitatively into the corresponding benzyluracils melting at 175° and 173° , respectively, by hydrolysis with hydrochloric acid.

The structures of the benzyluracils and incidentally of the mercaptopyrimidines were established in the following manner: The benzyluracil melting at 173° reacted with methyl iodide, giving 1-methyl-3-benzyluracil, XVI. This same pyrimidine was also obtained by the action of benzyl chloride on 1-methyluracil,¹ XVIII. This benzyl derivative is therefore to be represented as 3-benzyluracil, XIII., and the isomer, melting at 175° , as 1-benzyluracil, XII. The mercaptopyrimidines, melting at 77° and 139° , are therefore to be assigned the structural formulas IX. and X., viz., 1-benzyl-2-ethylmercapto-6-oxypyrimidine and 2-ethylmercapto-3-benzyl-6-oxypyrimidine, since they are converted into 1-benzyluracil, XII., and 3-benzyluracil, XIII., respectively, by hydrolysis with acids.

2-Ethylmercapto-5-brom-6-oxypyrimidine² reacted with benzyl chloride, giving an excellent yield of 2-ethylmercapto-3-benzyl-5-brom-6-oxypyrimidine, XI. This was converted

¹ Johnson and Heyl: *Loc. cit.*

² THIS JOURNAL, 31, 603.

quantitatively into 3-benzyl-5-bromuracil, XIV., by hydrolysis with hydrochloric acid. The same pyrimidine was also formed by the action of bromine on 3-benzyluracil, XIII. 1-Methyl-3-benzyl-5-bromuracil, XVII., was formed by treatment of 3-benzyl-5-bromuracil, XIV., with methyl iodide, in presence of alkali, and also by the action of bromine on 1-methyl-3-benzyluracil, XVI.

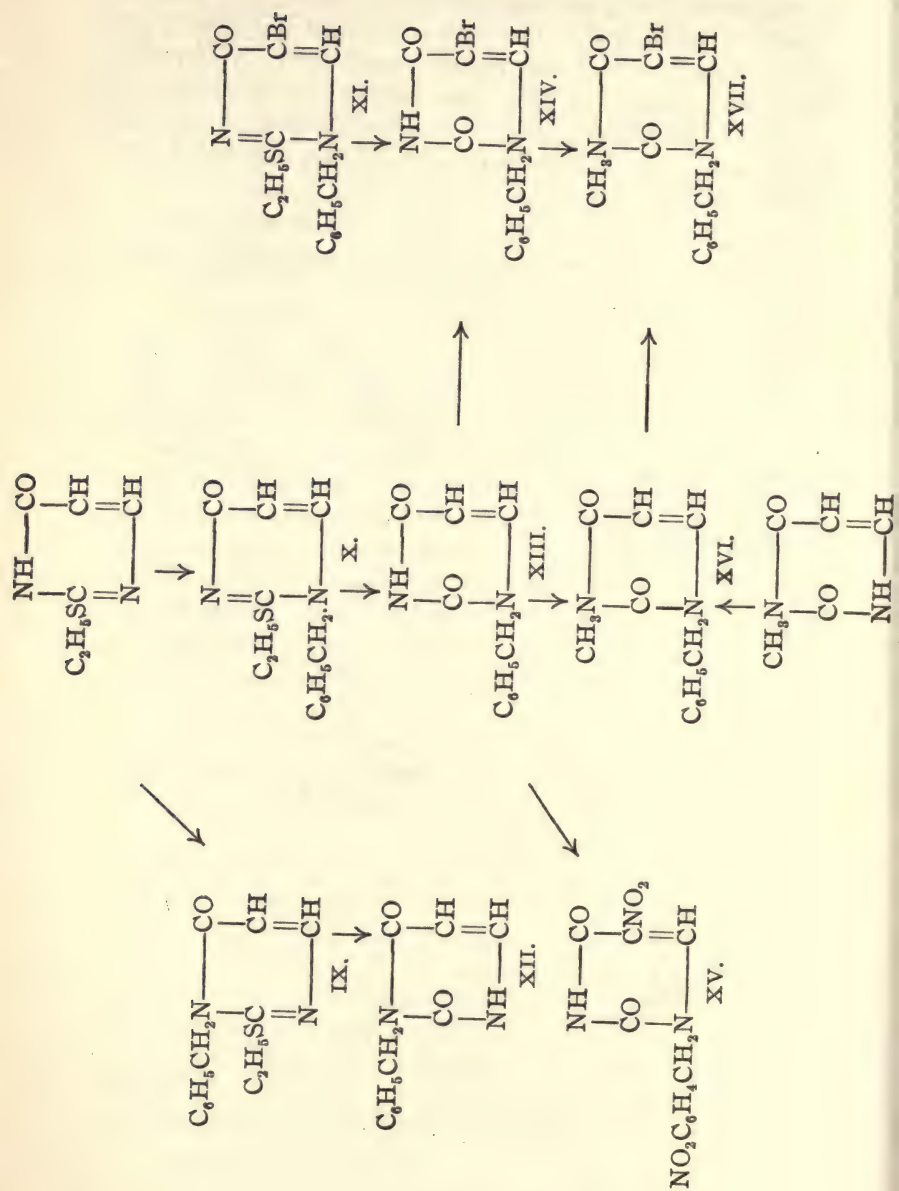
3-Benzyluracil, XIII., reacted with cold, fuming nitric acid, giving a dinitropyrimidine which we have provisionally represented as 3-*p*-nitrobenzyl-5-nitrouracil, XV.

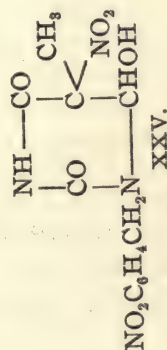
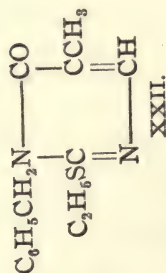
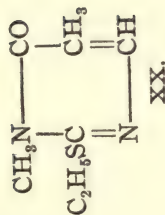
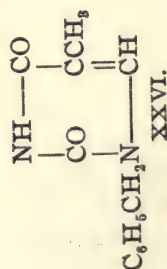
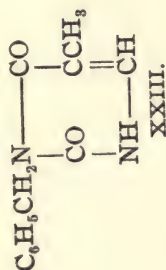
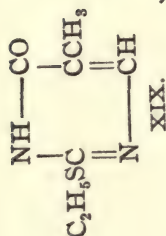
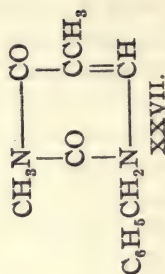
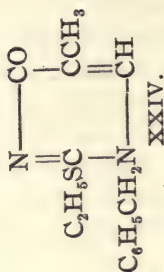
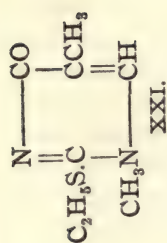
Johnson and Clapp¹ observed that 2-ethylmercapto-5-methyl-6-oxypyrimidine, XIX., reacted with methyl iodide, in presence of alkali, giving about equal proportions of 1,5-dimethyl-2-ethylmercapto-6-oxypyrimidine, XX., and 2-ethylmercapto-3,5-dimethyl-6-oxypyrimidine, XXI. We now find that benzyl chloride reacts with this mercaptopyrimidine, under the same conditions, giving 1-benzyl-2-ethylmercapto-5-methyl-6-oxypyrimidine, XXII., melting at 72°, and 2-ethylmercapto-3-benzyl-5-methyl-6-oxypyrimidine, XXIV., melting at 121°–122°. These pyrimidines were converted quantitatively into 1-benzylthymine, XXIII., melting at 205°, and 3-benzylthymine, XXVI., melting at 159°–160°, by hydrolysis with concentrated hydrochloric acid.

The structures of these four pyrimidines was determined by the behavior of the two benzylthymines towards diazobenzene-sulphonic acid. Johnson and Clapp² have shown in a recent paper that this reagent can be used to distinguish between 1- and 3-alkyl derivatives of uracil and thymine. They observed, for example, that 1-alkyl derivatives of these pyrimidines reacted with this reagent, giving red colored solutions. The isomeric 3-alkylpyrimidines, on the other hand, did not react with the diazo acid with the formation of red colors. We now find that the benzylthymine, melting at 205°, reacts with the sulphonic acid, giving a brilliant red solution, indicating that it is a 1-benzylthymine as represented by formula XXIII. The isomer gave no color with the sulphonic acid and therefore

¹ *Loc. cit.*

² *J. Biol. Chem.*, Vol. 5.





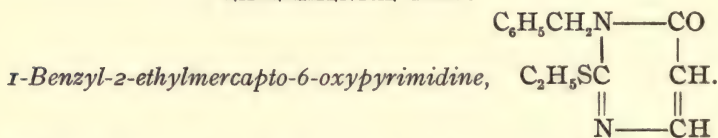
is to be assigned formula XXVI. The corresponding mercaptopyrimidines melting at 72° and 121° – 122° must therefore be represented by formulas XXII. and XXIV., respectively.

It is of interest to note here that the structures of the above benzyluracils, XII. and XIII., can also be determined by means of the diazo reagent. 1-Benzyluracil, XII., reacted with the acid, in presence of sodium hydroxide, giving a permanent red color, while its isomer, XIII., did not give a red color under the same conditions.

1-Methyl-3-benzylthymine, XXVII., was formed by the action of methyl iodide on 3-benzylthymine, XXVI. When the latter pyrimidine, XXVI., was dissolved in cold, fuming nitric acid of density 1.5 it was converted into a hydropyrimidine,¹ XXV., viz., 3-*p*-nitrobenzyloxynitrohydrothymine.

The four pyrimidines, 1-benzyluracil, 3-benzyluracil, 1-benzylthymine, and 3-benzylthymine, are characterized by their insolubility in cold water. 3-Benzyluracil and 3-benzylthymine are less soluble in water than uracil and thymine. They all crystallize from hot water without water of crystallization. They are weak acids and can be heated above their melting points without decomposition.

EXPERIMENTAL PART.



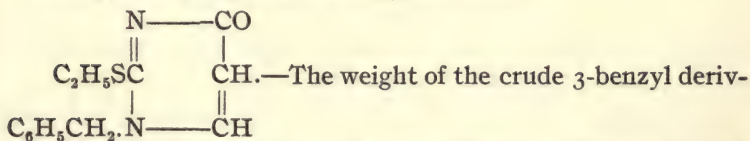
—Fifteen grams of 2-ethylmercapto-6-oxypyrimidine and 5.4 grams of finely pulverized potassium hydroxide were dissolved in about 75 cc. of boiling absolute alcohol. Twelve and two-tenths grams of benzyl chloride were then added and the solution heated on the steam bath until it gave no alkaline reaction with moist turmeric paper (about 4 hours). After cooling, the undissolved potassium chloride was filtered off and the alcohol removed by evaporation on the steam bath. We obtained a crystalline product which was triturated with 50 cc. of a 5 per cent solution of sodium hydroxide to remove un-

¹ Johnson: THIS JOURNAL, 40, 19; J. Biol. Chem., 4, 407.

altered pyrimidine and potassium chloride. When the alkaline solution was acidified with acetic acid we recovered 1.7 grams of 2-ethylmercapto-6-oxypyrimidine. The crystalline material, insoluble in sodium hydroxide, was then extracted thoroughly with an excess of ether and the insoluble material saved (see 3-benzyl derivative below). When the ether solution was allowed to evaporate we obtained some oil and about 3.0 grams of crystalline material which melted at 65°–70° to a clear oil with no effervescence. The oil gradually assumed a crystalline form on standing. The pyrimidine separated from alcohol in well-developed prisms melting at 77°. The weight of one crystal, which was selected for analysis, was 0.3+ gram. Analysis (Kjeldahl):

	Calculated for $C_{18}H_{14}ON_2S$.	Found.
N	11.38	11.63

2-Ethylmercapto-3-benzyl-6-oxypyrimidine,

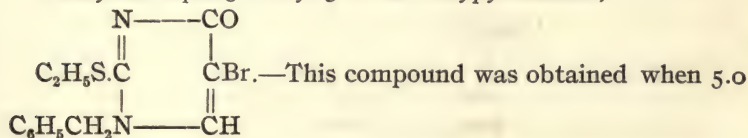


ative, insoluble in ether, in the above experiment, was 11.1 grams, corresponding to 51 per cent of the calculated. The pyrimidine is soluble in warm benzene, acetone, alcohol, very soluble in chloroform, and practically insoluble in cold ether and ligroin. It is difficultly soluble in hot water and crystallizes in long, slender prisms, and hexagonal prisms or flat tables melting at 139° to an oil. This melting point was not raised by recrystallization from benzene.

Analysis (Kjeldahl):

	Calculated for $C_{18}H_{14}ON_2S$.	I.	Found.	II.
N	11.38	11.58		11.61

2-Ethylmercapto-3-benzyl-5-brom-6-oxypyrimidine,



grams of 2-ethylmercapto-5-brom-6-oxypyrimidine¹ were heated in absolute alcohol, for 4 to 5 hours, with the required proportions of potassium hydroxide and benzyl chloride. After filtration from the undissolved potassium chloride and evaporation of the alcohol we obtained a semisolid substance which immediately solidified when washed with ether. The yield was 4.2 grams, corresponding to 60.0 per cent of the calculated. The pyrimidine is difficultly soluble in water and separates from a hot, aqueous solution in needles melting at 129° to a clear oil. Analysis (Kjeldahl):

N	Calculated for $C_{18}H_{18}ON_2BrS$.	Found.
	8.62	9.0

<i>1-Benzyluracil</i> ,	$C_6H_5CH_2.N \text{ --- } CO$	
	$\begin{array}{c} \\ CO \end{array}$	$\begin{array}{c} \\ CH \end{array} \text{ --- } A \text{ quantitative yield}$
	$\begin{array}{c} \\ NH \end{array}$	$\begin{array}{c} \\ CH \end{array}$
	$NH \text{ --- } CH$	

of this pyrimidine was obtained when 3.0 grams of the corresponding 2-mercaptopyrimidine were dissolved in 150 cc. of concentrated hydrochloric acid and the solution evaporated to dryness. It crystallizes from hot water in prismatic crystals melting at 175° to a clear oil. It did not contain water of crystallization. When mixed with the isomeric 3-benzyluracil (see below) melting at 173°, the fusion point was lowered to 140°-155°. The pyrimidine reacted with diazobenzenesulphonic acid, in presence of alkali, giving a red colored solution. Analysis (Kjeldahl):

N	Calculated for $C_{11}H_{10}O_2N_2$.	Found.
	13.86	14.1

<i>3-Benzyluracil</i> ,	$NH \text{ --- } CO$	
	$\begin{array}{c} \\ CO \end{array}$	$\begin{array}{c} \\ CH \end{array} \text{ --- } This \text{ pyrimidine was}$
	$\begin{array}{c} \\ C_6H_5CH_2.N \end{array}$	$\begin{array}{c} \\ CH \end{array}$
	$C_6H_5CH_2.N \text{ --- } CH$	

prepared by digesting 6.7 grams of 2-ethylmercapto-3-benzyl-6-oxypyrimidine with concentrated hydrochloric acid for 5 to 6

¹ Wheeler and Johnson: THIS JOURNAL, 31, 603.

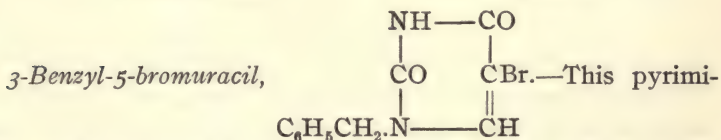
hours. The yield was 5.5 grams or 96 per cent of the theoretical. It crystallizes from alcohol in stout prisms melting at 173° to a clear oil with no effervescence. It is difficultly soluble in water and moderately soluble in cold acetone; insoluble in cold benzene and ether; and difficultly soluble in chloroform. It was insoluble in cold 25 per cent hydrochloric and sulphuric acids and easily soluble in warm glacial acetic acid. Analysis (Kjeldahl):

	Calculated for $C_{11}H_{10}O_2N_2$.	I.	Found.	II.
N	13.86	13.9		14.0

This pyrimidine does not react with diazobenzenesulphonic acid to give a red colored solution. The mixture assumed a yellow color, which was permanent for 30 minutes.

Solubility of 3-Benzyluracil in Water.—One hundred parts of water dissolved at 25°

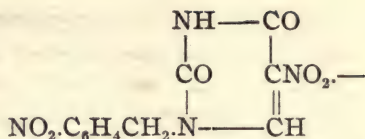
I.	II.
0.0998 gram.	0.1008 gram.



dine can be prepared by treating 3-benzyluracil in glacial acetic acid with the calculated quantity of bromine. It crystallizes from acetic acid in hexagonal prisms melting at 204° to a clear oil. The same brompyrimidine was also prepared by dissolving 0.5 gram of 3-benzyluracil in bromine water and allowing the solution to evaporate to dryness. The residue, about 0.8–0.9 gram, was then digested with absolute alcohol for 2 hours and the solution evaporated to dryness. The compound obtained by this treatment crystallized from alcohol in prisms melting at 204° . A quantitative yield of the pyrimidine was also obtained by digesting 2-ethylmercapto-3-benzyl-5-brom-6-oxypyrimidine with concentrated hydrochloric acid. Analysis (Kjeldahl):

	Calculated for $C_{11}H_9O_2N_2\text{Br}$.	Found.
N	9.96	10.0

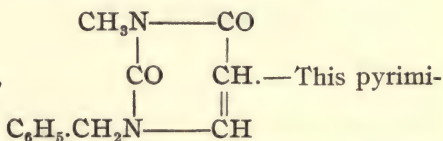
3-p-Nitrobenzyl-5-nitouracil,



Five-tenths of a gram of 3-benzyluracil was dissolved, at ordinary temperature, in 10 cc. of fuming nitric acid of density 1.5. The acid solution was then allowed to stand at ordinary temperature when prismatic crystals separated. They were purified for analysis by recrystallization from hot water. The pyrimidine is difficultly soluble and separates in slender prisms, which decompose, according to the rate of heating, at 235°–240° with effervescence. Analysis (Kjeldahl):

	Calculated for $\text{C}_{11}\text{H}_9\text{O}_6\text{N}_4$.	Calculated for $\text{C}_{11}\text{H}_9\text{O}_4\text{N}_3$.	I. Found.	II.
N	19.18	17.00	19.48	19.39

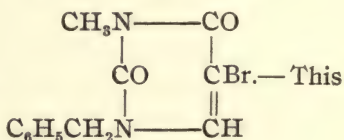
1-Methyl-3-benzyluracil,



dine is easily prepared by dissolving 3-benzyluracil and one molecular proportion of potassium hydroxide in alcohol and then warming with an excess of methyl iodide. The same pyrimidine was also obtained when 1-methyluracil¹ was digested in alcohol with the calculated proportions of potassium hydroxide and benzyl chloride. The pyrimidine is extremely soluble in alcohol and benzene. It crystallizes from dilute alcohol in needles melting at 75° to an oil without effervescence. Analysis (Kjeldahl):

	Calculated for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_2$.	I. Found.	II.
N	12.96	13.17	13.12

1-Methyl-3-benzyl-5-bromuracil,



pyrimidine was prepared in two ways:

¹ Johnson and Heyl: *Loc. cit.*

1. By dissolving 1-methyl-3-benzyluracil in glacial acetic acid and then adding the calculated amount of bromine. They reacted with evolution of heat. The pyrimidine was very soluble in glacial acetic acid but was precipitated by diluting with water.

2. By warming 0.8 gram of 3-benzyl-5-bromuracil in methyl alcohol with 1.9 grams of methyl iodide and 0.1 gram of metallic sodium. The alkylation was very smooth and the solution was neutral in a few minutes. The pyrimidine crystallizes from alcohol in diamond-shaped prisms melting at 123° to a clear oil with no effervescence. Analysis (Kjeldahl):

Calculated for
 $C_{12}H_{11}O_2N_2Br$.

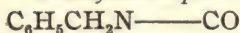
Found.

N

9.50

9.8

2-Ethylmercapto-1-benzyl-5-methyl-6-oxypyrimidine,



—Fifteen grams of 2-ethylmercapto-5-

methyl-6-oxypyrimidine and 4.9 grams of finely pulverized potassium hydroxide were dissolved in 75 cc. of absolute alcohol. Eleven and two-tenths grams of benzyl chloride were then added and the solution heated on the steam bath for 6 hours. After filtering from undissolved potassium chloride and evaporation of the alcohol we obtained a crystalline product which was washed with 50 cc. of a 5 per cent solution of sodium hydroxide. Four and four-tenths grams of unaltered pyrimidine deposited when the sodium hydroxide solution was acidified with acetic acid. The crystalline material, insoluble in sodium hydroxide, was then extracted in the usual manner with ether and the insoluble portion saved (see 3-benzyl derivative below). From the ether washings we obtained about 3.0 grams of pyrimidine melting at 65° – 66° . The compound is very soluble in acetone, benzene, and ether. It separates from dilute alcohol in stout prisms melting at 70° to a clear oil without effervescence. Analysis (Kjeldahl):

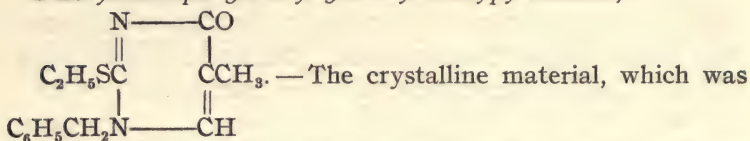
Calculated for
 $C_{14}H_{16}ON_2S$.

Found.

N

10.77

10.9

2-Ethylmercapto-3-benzyl-5-methyl-6-oxypyrimidine,

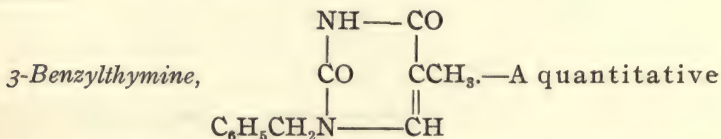
insoluble in ether, in the above experiment represented this pyrimidine and weighed 11.2 grams, corresponding to 68 per cent of the calculated. The pyrimidine is extremely soluble in alcohol and acetone. It was purified for analysis by recrystallization from benzene. It separated in hexagonal plates melting at 121°–122°. Analysis (Kjeldahl):

	Calculated for $\frac{1}{2}$ $\text{C}_{14}\text{H}_{16}\text{ON}_2\text{S}$.	Found.
N	10.77	11.1
<i>1-Benzylthymine,</i>	$ \begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2\text{N} \text{---} \text{CO} \\ \qquad \\ \text{CO} \qquad \text{CCH}_3 \text{---} \text{One and eight-} \\ \qquad \\ \text{NH} \text{---} \text{CH} \end{array} $	

tenths grams of 1-benzyl-2-ethylmercapto-5-methyl-6-oxypyrimidine were digested with concentrated hydrochloric acid until the evolution of ethyl mercaptan ceased. When this solution was evaporated to dryness the benzylthymine was obtained as a crystalline compound. The pyrimidine separated from hot alcohol in clusters of radiating prisms which melted at 204°–205° to a clear oil. The pyrimidine is difficultly soluble in water. Analysis (Kjeldahl):

	Calculated for $\text{C}_{13}\text{H}_{12}\text{O}_2\text{N}_2$.	Found.
N	12.96	13.3

This compound reacted with diazobenzenesulphonic acid, in presence of sodium hydroxide, giving a beautiful, claret red solution.



yield of this pyrimidine was obtained when the corresponding

2-mercaptopyrimidine was digested with concentrated hydrochloric acid until the evolution of ethyl mercaptan ceased. The pyrimidine is easily soluble in alcohol, acetone, benzene, and difficultly soluble in ether. It is very soluble in glacial acetic acid and chloroform and difficultly soluble in cold 25 per cent hydrochloric and sulphuric acids. It separates from hot water in diamond-shaped prisms melting at 160° to a clear oil with no effervescence. Analysis (Kjeldahl):

	Calculated for $C_{12}H_{12}O_2N_2$.	Found.
N	12.96	13.2

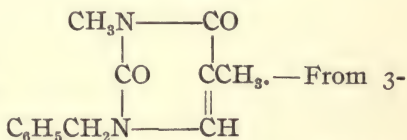
This pyrimidine did not react with diazobenzenesulphonic acid to give a red color. The mixture assumed a yellow color which remained permanent for over one hour.

Solubility of 3-Benzylthymine in Water.—One hundred parts of water dissolved at 25°

I.
0.1172 gram.

II.
0.1174 gram.

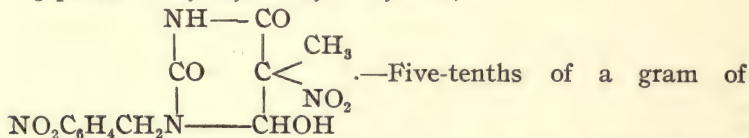
1-Methyl-3-benzylthymine,



benzylthymine and methyl iodide. It crystallized from water in prismatic crystals melting at 101° to a clear oil. It did not react with diazobenzenesulphonic acid to give a red color. Analysis (Kjeldahl):

	Calculated for $C_{13}H_{14}O_2N_2$.	Found.
N	12.17	12.07

3-p-Nitrobenzyloxynitrohydrothymine,



3-benzylthymine was dissolved in 10 cc. of cold fuming nitric acid of density 1.5. There was only slight evolution of heat

and the pyrimidine dissolved to a clear, yellow solution. On standing exposed to the atmosphere well-developed prisms separated. They decomposed at 176° with violent effervescence. A nitrogen determination indicated that a nitro group had entered the benzene ring and that nitric acid had added to the double bond in the 4,5 positions of the pyrimidine ring. Analysis (Kjeldahl):

	Calculated for			Found.
	$C_{12}H_{12}O_7N_4$.	$C_{13}H_{13}O_5N_3$.	$C_{12}H_{11}O_4N_3$.	
N	17.28	14.33	16.0	17.11

NEW HAVEN, CONN.,
June, 1908.

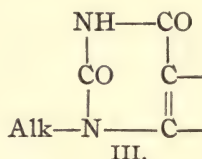
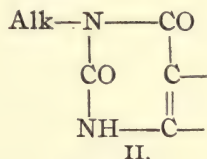
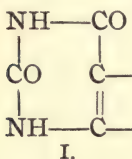
[Contributions from the Sheffield Laboratory of Yale University.]

CLXIII.—RESEARCHES ON PYRIMIDINES:
SYNTHESES OF NEW DERIVATIVES OF 5-HYDROXY-
URACIL (ISOBARBITURIC ACID).

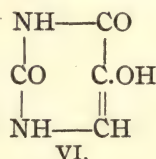
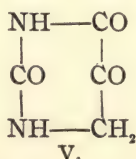
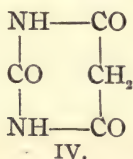
[THIRTY-NINTH PAPER.]

BY TREAT B. JOHNSON AND D. BREESE JONES.

Johnson and Clapp¹ have shown that 1- and 3-alkyl derivatives of 2,6-dioxytetrahydropyrimidines, I., can be distinguished by the difference in their behavior towards diazobenzene-sulphonic acid. The 1-alkylpyrimidines, II., react with the sulphonic acid, in presence of alkali, giving red colored solutions, while the isomeric 3-alkylpyrimidines, III., do not give red colors under the same conditions. This interesting behavior of 1-alkylpyrimidines enabled Johnson and Derby² to determine the structures of the isomeric 1- and 3-benzyl derivatives of uracil and thymine.



We have also found this diazo reagent to be of service for determining the structures of some new 1- and 3-alkyl derivatives of isobarbituric acid. The name—*isobarbituric*—signifies a compound isomeric with barbituric acid, IV., and having the constitution of a hexahydropyrimidine, as represented by formula V. The reactions of this pyrimidine, however, do not indicate a hexahydro compound but rather a tetrahydropyrimidine, as represented by formula VI., viz., *5-hydroxyuracil*.

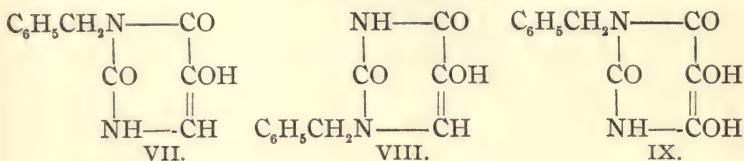


¹ J. Biol. Chem., 5, 163 (1908).

² THIS JOURNAL, 40, 444 (1908).

Formula VI. is supported by the facts that the pyrimidine does not give an oxime¹ and also that the hydrogen of the 5-hydroxyl group is replaceable by the acetyl radical² when the pyrimidine is warmed with acetic anhydride. Furthermore, the pyrimidine and its ethyl ether³ react with diazobenzenesulphonic acid, giving red colors as intense as that obtained with thymine.⁴

We shall describe in this paper the preparation and properties of 1-benzyl-5-hydroxyuracil (1-benzylisobarbituric acid), VII., 3-benzyl-5-hydroxyuracil (3-benzylisobarbituric acid), VIII., and also 1-benzylisodialuric acid, IX.



Johnson and McCollum⁵ have shown that pseudoethylthio-urea condenses smoothly with the sodium salt of ethyl α -ethoxy- β -oxyacrylate, giving 2-ethylmercapto-5-ethoxy-6-oxypyrimidine, X. This mercaptopyrimidine reacted with benzyl chloride, in presence of alkali, giving two isomeric pyrimidines, *viz.*, 1-benzyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine, XII., melting at 140°–141°, and 2-ethylmercapto-3-benzyl-5-ethoxy-6-oxypyrimidine, XIII., melting at 85°–86°. We did not observe the formation of 2-ethylmercapto-5-ethoxy-6-benzoxypyrimidine, XI. These two mercaptobenzylpyrimidines, XII. and XIII., were converted smoothly by hydrolysis with hydrochloric and hydrobromic acids into 1-benzyl-5-hydroxyuracil, XVII., melting at 230°, and 3-benzyl-5-hydroxyuracil, XIX., melting at 200°–210°, respectively. We also succeeded in isolating the two intermediate products of the hydrolysis, *viz.*, 1-benzyl-5-ethoxyuracil, XIV., melting at 150°, and 3-benzyl-5-ethoxyuracil, XVI., melting at 163°–164°.

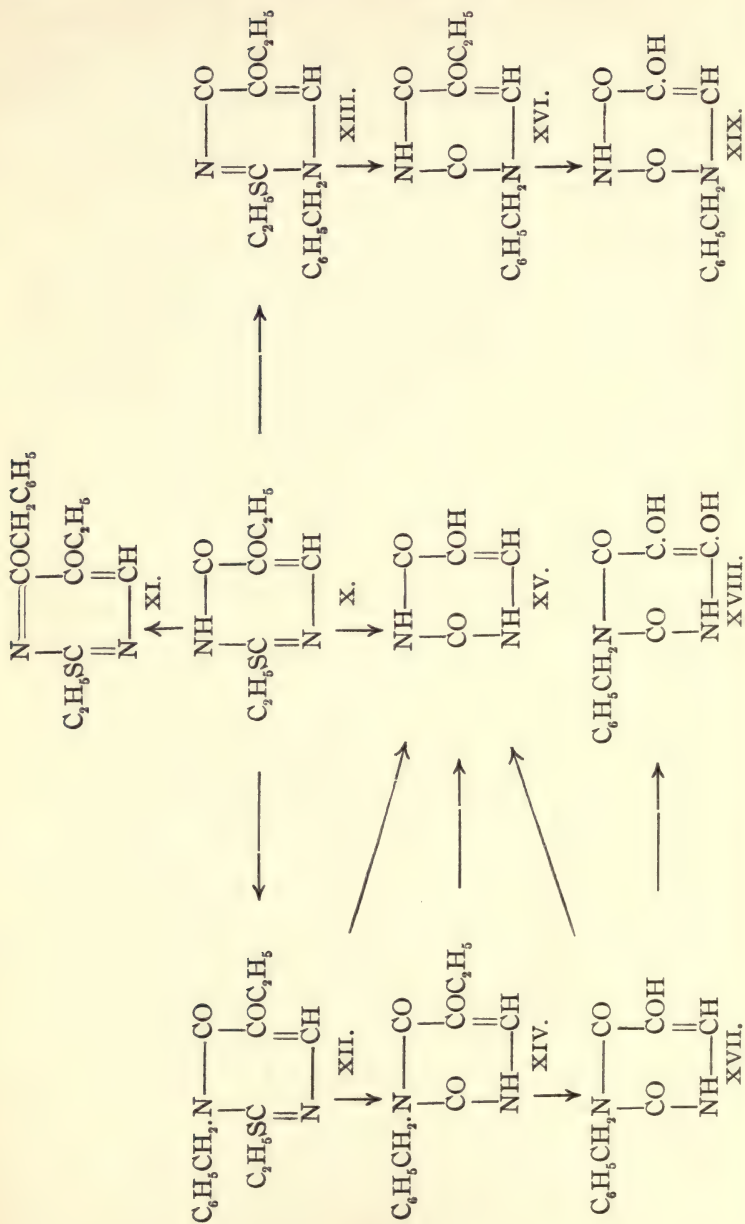
¹ Behrend and Roosen: *Ann. Chem.* (Liebig), **251**, 240.

² Behrend and Roosen: *Loc. cit.*

³ Johnson and McCollum: *J. Biol. Chem.*, **1**, 437; *THIS JOURNAL*, **36**, 154.

⁴ Johnson and Clapp: *Loc. cit.*

⁵ *Loc. cit.*

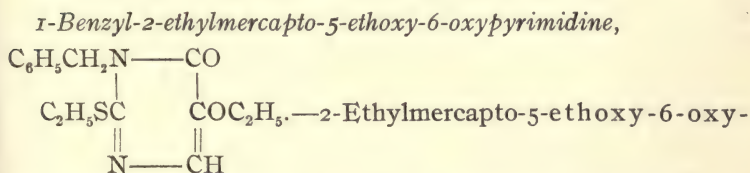


The structures of these pyrimidines were established in the following manner: The 1-benzyl-5-hydroxyuracil, XVII., melting at 230°, and the corresponding ethyl ether, XIV., reacted with diazobenzenesulphonic acid in presence of sodium hydroxide, giving beautiful red colors. The isomeric benzyl hydroxyuracil, XIX., melting at 200°–210°, and its ethyl ether, XVI., did not react with the sulphonic acid, with formation of red colors, indicating that these pyrimidines are 3-benzyl derivatives, as represented by the formulas above.

The benzyl-5-hydroxyuracils and their ethyl ethers are difficultly soluble in water. The hydroxyuracils are weak acids and stable in the presence of hydrochloric acid below 100°. 1-Benzyl-5-hydroxyuracil, XVII., was converted practically quantitatively into 5-hydroxyuracil (isobarbituric acid), XV., when heated with concentrated hydrochloric acid at 150°–160°.

1-Benzyl-5-hydroxyuracil, XVII., was converted quantitatively into 1-benzylisodialuric acid, XVIII., when it was suspended in cold water and then dissolved by adding a molecular proportion of bromine. The isodialuric acid crystallized from hot water without decomposition and gave a violet colored salt with barium hydroxide.

EXPERIMENTAL PART.



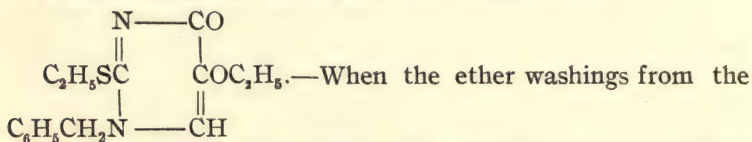
pyrimidine¹ (34 grams) and one molecular proportion of potassium hydroxide (9.0 grams) were dissolved in 250 cc. of boiling, absolute alcohol. Twenty-one and five-tenths grams of benzyl chloride were then added and the solution boiled until it gave no alkaline reaction when tested with moist turmeric (about 2 to 2.5 hours). The undissolved potassium chloride was then separated by filtration and the excess of

¹ Johnson and McCollum: *Loc. cit.*

alcohol removed by evaporation on the steam bath. We obtained a syrup which completely solidified after trituration with about 30 to 50 cc. of a 10 per cent solution of sodium hydroxide. When the alkaline solution was acidified with acetic acid we recovered 3.8 grams of the unaltered 2-ethylmercaptopyrimidine. The crude benzylpyrimidines were then extracted 3 times with boiling ether and the ether solutions saved (see 3-benzyl derivative below). The 1-benzylpyrimidine was insoluble in ether and melted without further purification at 134° – 136° to an oil. It was purified for analysis by recrystallization from acetone or hot water. It separated in slender prisms melting at 140° – 141° to an oil without effervescence. The compound is very soluble in alcohol, benzene, and acetone. It crystallizes from water in anhydrous condition. Analysis (Kjeldahl):

	Calculated for $C_{15}H_{18}O_2N_2S$.	I.	Found.	II.
N	9.65	9.81		9.80

2-Ethylmercapto-3-benzyl-5-ethoxy-6-oxyprymidine,



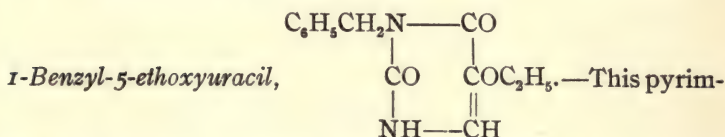
above experiment were heated on the steam bath to remove the ether we obtained a syrup which partially solidified after standing for 3 to 4 days. The crystalline material was separated from a small amount of oil by suction filtration and recrystallized from 95 per cent alcohol. It deposited, on cooling, in heavy, prismatic crystals which melted at 85° – 86° to a clear oil with no effervescence. The pyrimidine is very soluble in acetone, alcohol, and ether, but insoluble in cold water. Analysis (Kjeldahl):

	Calculated for $C_{15}H_{18}O_2N_2S$.	Found.
N	9.65	9.30

The total yields, and relative proportions of the crude isomeric benzylpyrimidines obtained in 4 experiments by alkyla-

tion of the mercaptopyrimidine, are given in the following table:

	Weight of 2-ethyl- mercaptopyrim- idine taken. Grams.	Weight of crude 1-benzyl deriva- tive obtained. Grams.	Weight of crude 3-benzyl deriva- tive obtained. Grams.	Weight of un- altered 2-ethyl- mercaptopyrim- idine recovered. Grams.	Percentage yield of 1- and 3-benzyl derivatives.
1	47.5	36.0 or 59.3%	24.7 or 40.7%	2.5	93.4
2	34.0	23.5 or 57.3%	17.5 or 42.7%	3.8	94.0
3	18.0	16.0 or 80.0%	4.0 or 20.0%	3.0	92.5
4	5.0	4.5	..	..	..



idine was always obtained mixed with 1-benzyl-5-hydroxyuracil (see below) by hydrolysis of 1-benzyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine with concentrated hydrochloric acid. In one experiment, 5 grams of the mercaptopyrimidine were dissolved in 150 cc. of concentrated hydrochloric acid and the solution boiled for 12 hours. When the hydrochloric acid was removed, by heating on the steam bath, we obtained a mixture of the ethoxypyrimidine and benzylhydroxyuracil melting at 140°–180°. They were separated from each other by fractional crystallization from 95 per cent alcohol. This pyrimidine was more soluble in alcohol than the hydroxyuracil and crystallized in characteristic hexagonal prisms melting at 150° to an oil. This melting point was not raised by recrystallization from water. The pyrimidine did not contain water of crystallization and did not give a test for sulphur. When

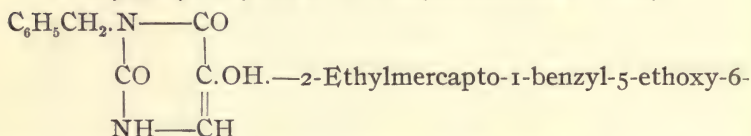
it was dissolved in bromine water, and barium hydroxide added to the solution, a purple precipitate was obtained.

The pyrimidine reacted with diazobenzenesulphonic acid, in presence of sodium hydroxide, giving a brilliant, red colored¹ solution. The color slowly faded on standing. Analysis:

0.1160 gram of substance gave 11.8 cc. N at 19° and 759 mm.

	Calculated for $C_{13}H_{14}O_3N_2$.	Found.
N	11.38	11.6

1-Benzyl-5-hydroxyuracil (1-Benzylisobarbituric Acid),



oxypyrimidine is not converted quantitatively into this pyrimidine by boiling with hydrochloric acid. In order to obtain a complete hydrolysis within a few hours we found it necessary to proceed under the following conditions: 36 grams of the mercaptopyrimidine were dissolved in about 500 cc. of concentrated hydrochloric acid and the solution evaporated to dryness. We obtained a crystalline mixture of the intermediate ethoxypyrimidine (see above) and the benzylhydroxyuracil, which was then dissolved in 40 to 50 cc. of hydrobromic acid. After 3 to 4 hours' digestion with this acid the hydrolysis was complete. Too long digestion with hydrobromic acid is not advisable because the benzylhydroxyuracil slowly undergoes decomposition with formation of benzyl bromide and 5-hydroxyuracil. After removal of the hydrobromic acid the pyrimidine was purified by several recrystallizations from alcohol and water. The yield was good. The pyrimidine is less soluble in alcohol than the corresponding ethoxy derivative (see above). It crystallizes from alcohol in clusters of radiating prisms melting at 230° to an oil with effervescence. The pyrimidine separates from hot water in corpuscular crystals resembling in appearance the crystalline form of 5-hydroxyuracil (Analysis III.). A violet purple precipitate was obtained when the

¹ Johnson and Clapp: *Loc. cit.*

pyrimidine was dissolved in bromine water and barium hydroxide added to the solution. The pyrimidine reacts with diazobenzenesulphonic acid, in presence of sodium hydroxide, giving as intense a red color as 1-benzyl-5-ethoxyuracil. Analyses:

I. 0.0925 gram substance gave 10.2 cc. N at 19° and 756 mm.

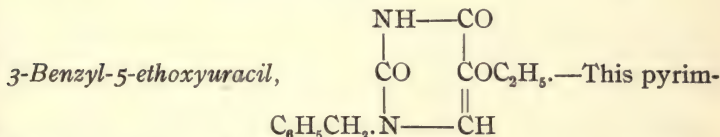
II. and III. Nitrogen by Kjeldahl method.

	Calculated for $C_{11}H_{10}O_3N_2$.	I.	Found. II.	III.
N	12.84	12.60	12.95	13.0

5-Hydroxyuracil (Isobarbituric Acid) from 1-Benzyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine.—About 3.5 grams of the mercaptopyrimidine were dissolved in 50 cc. of concentrated hydrochloric acid and the solution heated for 3 hours at 150°–160°. When the tube was opened there was no pressure, and oil floated on the surface of the solution. This was separated and identified as a mixture of ethyl mercaptan and benzylchloride. When the acid solution was evaporated to dryness, we obtained a colorless substance which was difficultly soluble in water. It crystallized from hot water in hard, corpuscular crystals, which decomposed without melting at about 300°. It did not contain sulphur and chlorine. When the compound was dissolved in bromine water and barium hydroxide added to the solution, a purple precipitate was obtained. A nitrogen determination agreed with the calculated value for 5-hydroxyuracil.¹

0.1321 gram substance gave 25.4 cc. N at 22° and 750 mm.

	Calculated for $C_4H_4O_3N_2$.	Found.
N	21.87	21.48



idine was formed smoothly when 2-ethylmercapto-3-benzyl-5-ethoxy-6-oxypyrimidine was digested with con-

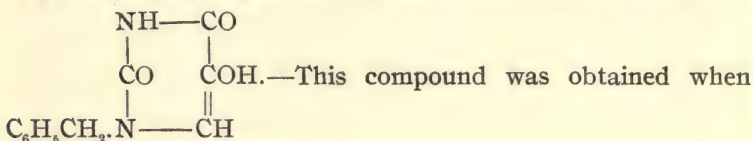
¹ Behrend and Roosen: *Loc. cit.*

centrated hydrochloric acid. It appeared to be more stable, in presence of hydrochloric acid, than the isomeric 1-benzylpyrimidine. The compound is difficultly soluble in cold water but separates from a hot solution in needlelike prisms. It is very soluble in alcohol and separates from this solvent in the form of plates. It melts at 163° – 164° to a clear oil. When the pyrimidine is dissolved in bromine water and barium hydroxide is added to the solution a violet precipitate is obtained. The pyrimidine did not react with diazobenzene-sulphonic acid to give a red colored solution. The solution assumed a yellow color which was permanent for 20 minutes.

Analysis (Kjeldahl):

	Calculated for $C_{13}H_{14}O_5N_2$.	I.	Found. II.
N	11.38	11.23	11.40

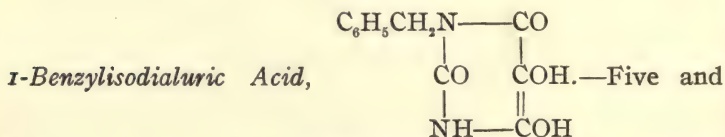
3-Benzyl-5-hydroxyuracil (*3-Benzylisobarbituric Acid*),



2-ethylmercapto-3-benzyl-5-ethoxy-6-oxypyrimidine was digested for several hours with hydrobromic acid. The pyrimidine crystallized from acetic acid in irregular crystals which melted from 200° to 210° according to the rate of heating. It was difficultly soluble in water and alcohol.

Analysis (Kjeldahl):

	Calculated for $C_{11}H_{10}O_5N_2$.	Found.
N	12.84	12.63



eight-tenths grams of finely pulverized 1-benzyl-5-hydroxyuracil were suspended in 50 cc. of ice water, and 4.5 grams of bromine slowly added to the solution with constant stirring. The bromine immediately disappeared and the pyrimidine

completely dissolved. The excess of water was then removed by distillation under diminished pressure at a temperature of 50° to 70° . The isodialuric acid finally separated from the warm, saturated solution in beautiful, prismatic crystals. The solution was then cooled and the crystals separated by filtration. The yield of crude material was 6.1 grams. The pyrimidine is very soluble in hot water and separates, on cooling, in lenticular crystals melting at 139° with effervescence. The pyrimidine dissolved in a solution of barium hydroxide with formation of a violet colored solution. When heated at 105° the pyrimidine slowly underwent decomposition.

Analysis:

0.0979 gram substance gave 10 cc. of N. at 20° and 768 mm.

	Calculated for $C_{11}H_{10}O_4N_2$.	Found.
N	11.96	11.81

NEW HAVEN, CONN.,
June, 1908.

[Reprinted from the American Chemical Journal, Vol, XL,
No. 6. December, 1908.]

[Contributions from the Sheffield Laboratory of Yale University.]

CLXIV.—RESEARCHES ON PYRIMIDINES:
THE THIO DERIVATIVES OF URACIL AND THE PREP-
ARATION OF URACIL IN QUANTITY.

[FORTIETH PAPER.]

BY HENRY L. WHEELER AND LEONARD M. LIDDLE.

The impression is given in several text-books that the preparation of uracil, thymine, and cytosine by our synthetic methods¹ is no easier than the isolation of these substances from nucleic acids. Our syntheses are even given in Beilstein² as a process of formation (*Bildung*) and not as the best method of preparation (*Darstellung*). This view of our work is far from correct. In the past few years we have prepared a number of kilograms of these pyrimidines by our methods. The preparation of this amount of these substances from the nucleic acids would be a task for a factory.

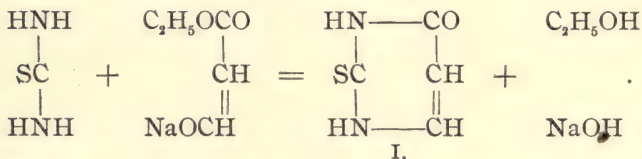
¹ Wheeler, Merriam, and Johnson: THIS JOURNAL, 29, 478 and 492 (1903).

² Ergänzungsbände, IV., 550, 551, 1162.

For the preparation of uracil the sodium salt of formylacetic ester, $\text{NaOCH}=\text{CHCO}_2\text{C}_2\text{H}_5$,¹ was condensed, in alkaline, aqueous solution, with a pseudothiurea, $\text{H}_2\text{N}-\text{C}(\text{SC}_2\text{H}_5)_2\text{NH}$. The condensation product, 2-ethylmercapto-6-oxypyrimidine, on boiling with hydrochloric acid, easily gave off mercaptan, and a quantitative yield of uracil was obtained.

In this paper we describe a method of preparing uracil that is an improvement even over our previous synthesis. It has been our experience that thiourea gives uniformly larger yields of pyrimidine derivative than ethylpseudothiurea² when condensed with the sodium salt of formylacetic ester.

The condensation with thiourea takes place with the formation of 2-thiouracil, I.,³ as follows:



This condensation has the advantage over our previous method of avoiding the presence of mercaptan and since 2-thiouracil is more than ten times less soluble than 2-ethylmercapto-6-oxypyrimidine it separates more nearly completely on acidifying.

It remained then to discover a simple method of replacing the sulphur in this substance by oxygen. 2-Thiouracil, like other compounds of this class, is not desulphurized readily, if at all, by the ordinary methods. It forms more or less stable salts with the metallic oxides. List had a similar ex-

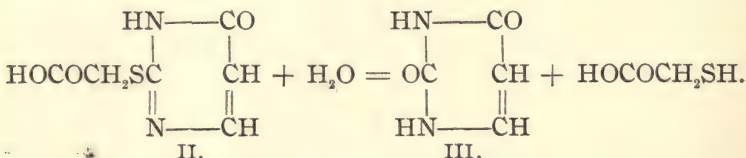
¹ Wislicenus: Ber. d. chem. Ges., **20**, 2931 (1887).

² We have repeated our earlier attempts to condense the sodium salt of ethyl formylacetate with urea in aqueous solution, and thus obtain uracil directly, but without success. We have found that pyrimidine condensations which fail when water is used as the solvent may be brought about in alcoholic solution, in the presence of sodium ethylate. When the sodium salt of ethyl formylacetate, urea, and sodium ethylate were warmed for an hour on the steam bath and then tested for uracil with bromine water and barium hydroxide (J. Biol. Chem., **3**, 183 (1907)) no color was obtained. No precipitate was formed on acidifying the concentrated solution and no evidence of the formation of uracil was observed.

³ Wheeler and Bristol: THIS JOURNAL, **33**, 458 (1905).

perience with 2-thio-4-methyluracil.¹ To desulphurize this substance it was necessary to heat in a closed tube with hydrochloric acid for a few hours at 150°–160°. The thiohydantoins evidently also belong to this class.²

After a number of experiments we found that when 2-thio-uracil was simply boiled with an aqueous solution of chloracetic acid, in slight excess, sulphur was easily removed, and on evaporation uracil remained. The yield was practically quantitative. The reaction probably involves the intermediate formation of the unstable 6-oxypyrimidine-2-thioglycollic acid, II., which, as we show below, on boiling with water gives uracil, III., and thioglycollic acid or its decomposition products, as follows:



This reaction, which introduces nothing which can not be easily removed, is so smooth and satisfactory that we intend to investigate the use of chloracetic acid for desulphurization in other cases. At present, we have examined simply the new thio derivatives of uracil in this respect and have made the curious observation that while 2-thiouracil and 6-thiouracil, VII., are readily desulphurized, 2,6-dithiouracil, VIII., is not desulphurized on boiling with chloracetic acid but apparently forms the stable pyrimidine, 2,6-dithioglycollic acid, IX.

The preparation of the new thio derivatives of uracil was carried out as follows: 2-Ethylmercapto-6-chlorpyrimidine, V., from 2-ethylmercapto-6-oxypyrimidine,³ IV., was treated with potassium hydrosulphide, giving 2-ethylmercapto-6-thiopyrimidine, VI.

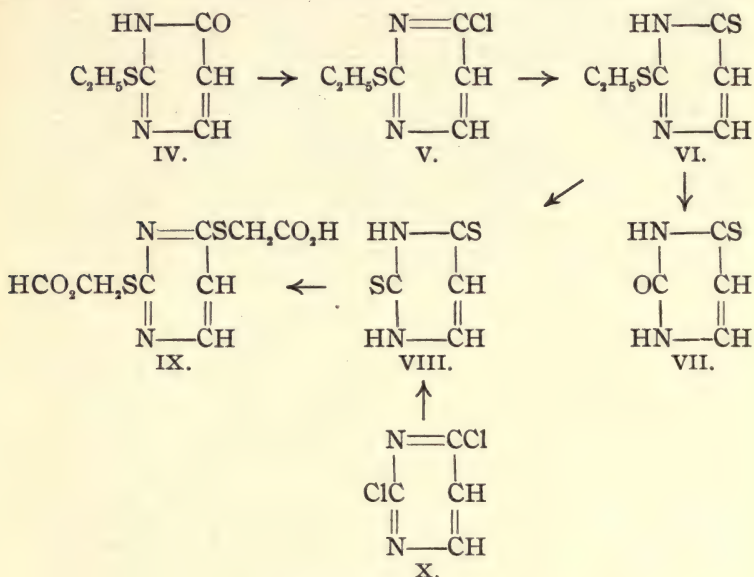
When this compound was treated with concentrated hydrochloric acid on the steam bath mercaptan was evolved and

¹ Ann. Chem. (Liebig), **236**, 1 (1886).

² Bailey and Randolph: Ber. d. chem. Ges., **41**, 2495 (1908).

³ Wheeler and Johnson: THIS JOURNAL, **29**, 496 (1903).

6-thiouracil, VII., was formed. On heating with dry hydrogen chloride, ethyl chloride was given off and 2,6-dithiouracil, VIII., was obtained. The latter was also prepared from 2,6-dichlorpyrimidine, X., and potassium hydrosulphide.



EXPERIMENTAL PART.

2-Thiouracil, $\begin{array}{c} \text{HN}-\text{CO} \\ | \quad | \\ \text{SC} \quad \text{CH} \\ | \quad || \\ \text{HN}-\text{CH} \end{array}$.—The sodium salt of formylacetic

ester, prepared according to Wislicenus¹ directions from 150 grams of ethyl formate, 150 grams of ethyl acetate, and 42 grams of sodium clippings in 500–600 cc. of dry ether, was dissolved in a cold, saturated, aqueous solution of 70 grams of thiourea. The solution was allowed to stand for an hour or so, then warmed on the steam bath, and finally cooled and acidified with acetic acid. Four such experiments gave about 280 grams of 2-thiouracil.

¹ Ber. d. chem. Ges., **20**, 2933 (1887).

A portion of this material was crystallized from water until it was obtained in colorless bunches of prismatic plates which melted with decomposition at about 340° . A solubility determination was then made as follows: The substance was placed in cold water and a rapid stream of air was drawn by suction, first through a wash bottle containing distilled water, and then through the solution containing the suspended substance. After two hours the undissolved material was filtered off and a weighed portion of the solution was evaporated to dryness and the residue was heated to constant weight at 110° .

To check the results a parallel series of determinations were made in which the substance was dissolved in hot water and the saturated solution was allowed to cool while air was drawn through for two hours as before. Solubility determinations were also made in this manner in the case of 2-ethylmercapto-6-oxypyrimidine and 2-methylmercapto-6-oxypyrimidine. It was found that 100 parts of water at 17° dissolved:

	Hot saturated solution.	Cold saturated solution.
2-Thiouracil	0.0533 gram	0.0598 gram
2-Methylmercapto-6-oxypyrimidine	0.6170 "	0.6620 "
2-Ethylmercapto-6-oxypyrimidine	0.8000 "	0.7930 "

The mercaptopyrimidines are therefore more than ten times as soluble in water as 2-thiouracil. 2-Thiouracil is almost insoluble in alcohol while the mercapto derivatives are very soluble. In our pyrimidine condensations alcohol is always present as a by-product, unless removed by evaporation; this reduces the yield in the case of the mercapto derivatives while in the case of thio derivatives just the opposite is true.

In accordance with its thioamide character, 2-thiouracil is a much stronger acid than uracil. It readily dissolves in sodium or potassium hydroxides and it forms very soluble, crystalline, anhydrous salts with these bases. It can be very conveniently crystallized from aqueous ammonia in which it is far more soluble than in water. It forms an ammonium salt which loses ammonia on drying or on boiling with water. Mercuric oxide removes 2-thiouracil from solution, forming an amorphous, anhydrous, insoluble salt.

The Copper Salt, $C_4H_2ON_2SCu.H_2O$.—Copper sulphate produces in aqueous solutions of 2-thiouracil, with or without alkali, an amorphous, mustard-yellow, insoluble precipitate. This salt can be boiled with water without alteration. It was dried in a desiccator over calcium chloride for analysis.

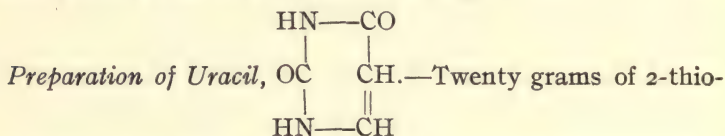
0.2997 gram substance lost 0.0276 gram on heating two hours at $105^\circ-115^\circ$.

	Calculated for $C_4H_2ON_2SCu.H_2O$.	Found.
H_2O	8.67	9.20

0.1167 gram substance gave 0.045 gram CuO .

	Calculated for $C_4H_2ON_2SCu.H_2O$.	Found.
Cu	30.60	30.76

When silver nitrate is added to an aqueous solution of 2-thiouracil an amorphous, gelatinous, white precipitate is formed which does not blacken on boiling.



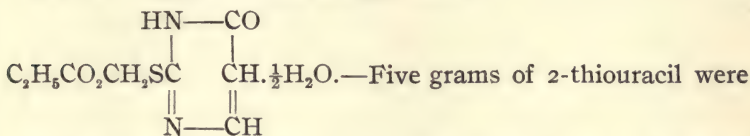
uracil were boiled with one and a half molecular proportions of chloracetic acid in a large amount of water for one hour, then evaporated to dryness on the steam bath. The slightly colored residue was decolorized by means of animal charcoal, and on concentrating the solution 14.2 grams of pure white uracil, free from sulphur, were obtained. The yield in this case was 81 per cent of the calculated. More could have been obtained from the mother liquor.

In another experiment 30 grams of 2-thiouracil were boiled with 33 grams of chloracetic acid in about 700 cc. of water. When the material had dissolved the solution was allowed to evaporate to dryness on the steam bath. The residue was warmed with alcohol, filtered, and washed with alcohol. It was then free from sulphur and weighed 23.5 grams. This is 89.5 per cent of the calculated.

Uracil from 6-Thiouracil.—An aqueous solution of 2.1 grams of 6-thiouracil was mixed with 3 grams of chloracetic acid and

the solution was then evaporated to dryness on the steam bath. When the residue was crystallized from water 1.2 grams of pure uracil separated. This is 66 per cent of the calculated.

Ethyl 6-Oxypyrimidine-2-thioglycollate,

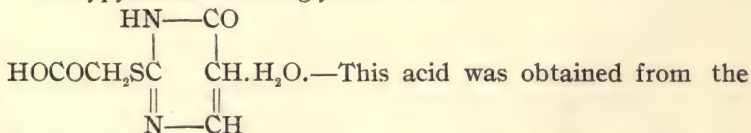


mixed with a solution of 0.9 gram of sodium in 30 cc. of alcohol and then 4.8 grams of ethyl chloracetate were added. The mixture was heated on the steam bath under a return condenser for one hour. The solution was then filtered and allowed to evaporate under reduced pressure in a desiccator. The crystalline residue after three recrystallizations from water yielded long, thin, glistening plates. These gave a strong test for sulphur and melted to a clear oil at 154°-155°. The substance was easily soluble in hot water and hot alcohol and nearly insoluble in cold water.

0.2852 gram substance lost 0.0138 gram when heated at 100°-115° for two hours.

	Calculated for $\text{C}_8\text{H}_{10}\text{O}_3\text{N}_2\text{S} \cdot \frac{1}{2}\text{H}_2\text{O}.$	I.	Found. II.	III.
H_2O	4.03			4.83
N	12.55	12.44	12.57	

6-Oxypyrimidine-2-thioglycollic Acid,



above ester by warming its aqueous solution with an excess of potassium hydroxide for a few minutes on the steam bath. The solution was then cooled and acidified with hydrochloric acid. A heavy, white precipitate formed which crystallized from water in bunches of fine prisms. This proved to be the hydrous form which separates slowly and melts at 178°. If the solution is stirred or the beaker scratched the anhydrous form generally results. The latter separates rapidly in loose

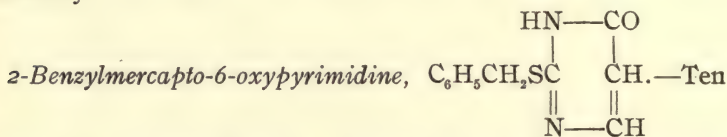
bunches of fine needles. The substance can be crystallized from alcohol. When it is boiled with water, thioglycollic acid separates and uracil is obtained.

0.2676 gram substance lost 0.0238 gram when heated two hours at 105° – 110° .

	Calculated for $C_6H_6O_3N_2S.H_2O$.	I.	Found. II.	III.
H_2O	8.82	8.89		
N	13.72		13.90	13.65

Some experiments were made with the object of preparing alkyl derivatives of 2-thiouracil. If a smooth alkylation on the sulphur would take place it would be the best method for the preparation of 2-alkylmercaptopyrimidines.

2-Ethylmercapto-6-oxypyrimidine.¹—The action of sodium ethylate and ethyl iodide on 2-thiouracil in alcoholic solution gave 2-ethylmercapto-6-oxypyrimidine, melting at 152° . When 30 grams or more of 2-thiouracil were employed the yields were much below the calculated. Unaltered 2-thiouracil was recovered when the substances were allowed to act in molecular proportions. It required repeated recrystallizations from alcohol to remove this impurity, so that the yields were unsatisfactory. If an excess of iodide and alkali were used the yield of 2-ethylmercapto-6-oxypyrimidine was still further reduced, owing to the formation of higher alkylated products. It was found that benzyl chloride acted more smoothly.



grams of 2-thiouracil and 4.4 grams of potassium hydroxide were dissolved in the smallest possible quantity of water on the steam bath and mixed with 9.9 grams of benzyl chloride. Alcohol was then added until the oil went into solution. The reaction took place immediately and gave long, slender, colorless prisms weighing 11.7 grams, or 68 per cent of the calculated.

¹ Wheeler and Merriam: THIS JOURNAL, 29, 478 (1903).

The same quantities of substances shaken repeatedly in a separatory funnel in aqueous solution without alcohol gave 12.4 grams, or 72 per cent of the calculated. The first method of preparation is smoother and is much easier, the product being more nearly pure.

The substance is soluble in about 16 parts of hot alcohol and in 50 parts of cold. In water or ether it is practically insoluble. Recrystallization from alcohol gave slender, twinned prisms which melted to a clear oil at 192° – 193° .

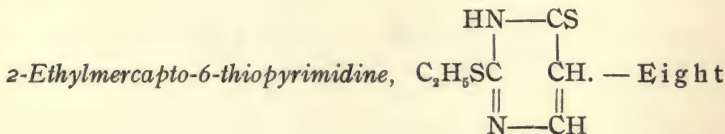
	Calculated for $C_{11}H_{10}ON_2S$.	Found.
N	12.88	12.88

When the substance was warmed with hydrochloric acid on the steam bath, benzyl mercaptan separated. On evaporating and extracting with alcohol, uracil was obtained.

The Sodium Salt of 2-Benzylmercapto-6-oxypyrimidine, $C_{11}H_9ON_2SNa \cdot 3H_2O$.—The mercapto derivative was dissolved in an aqueous solution of sodium hydroxide and allowed to crystallize slowly in a desiccator. Large talclike plates formed which were very soluble in water and fairly soluble in alcohol.

0.3069 gram of substance lost 0.056 gram when heated at 100° – 110° for two hours.

	Calculated for $C_{11}H_9ON_2SNa \cdot 3H_2O$.	I.	Found. II.	III.
H_2O	18.35	18.24		
N	9.52		9.69	9.43

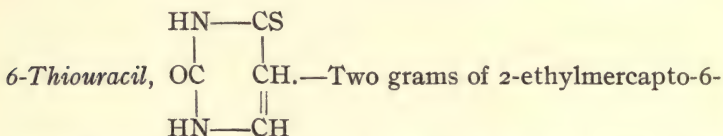


grams of 2-ethylmercapto-6-chlorpyrimidine¹ were treated with two and a half times the calculated quantity of potassium hydrosulphide in alcoholic solution. The solution was boiled for about 15 minutes and then evaporated to dryness on the steam bath and the residue taken up in a small quantity of

¹ Wheeler and Johnson: THIS JOURNAL, 29, 496 (1903); 31, 596 (1904).

water. The solution was shaken with ether, to remove any 6-ethoxy or unaltered chlor compound, and then made distinctly acid in the cold with acetic acid. A white flocculent precipitate separated, weighing 6.4 grams, or 80 per cent of the calculated. The substance was recrystallized twice from water, when it gave brilliant needlelike prisms, having a pale yellow color, which melted to a yellow oil at 149° . The material was easily soluble in alcohol and moderately in hot water. In cold water it was nearly insoluble. The properties of the compound were very similar to those of 2-ethylmercapto-6-oxypyrimidine, but a mixture of these substances melted at about 126° .

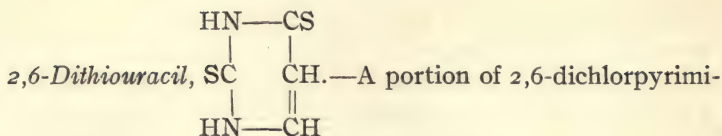
	Calculated for $C_6H_8N_2S_2$.	Found.
N	16.27	16.05



thiopyrimidine were evaporated to dryness on the steam bath with 10 cc. of concentrated hydrochloric acid. Mercaptan escaped. The residue was extracted with cold alcohol to remove unaltered ethylmercaptothiopyrimidine and the insoluble material was then found to weigh 0.8 gram, or 55 per cent of the calculated. In another experiment more prolonged action of acid gave a yield of 90.0 per cent; a small amount of uracil was also formed.

Like uracil and 2-thiouracil, 6-thiouracil is practically insoluble in strong alcohol but moderately soluble in hot water. It crystallized from hot water in small, light yellow needles. On rapidly heating it blackened above 270° and melted with effervescence at 328° . The properties of this substance are closely similar to those of 2,6-dithiouracil but a mixture of these compounds melted at 295° .

	Calculated for $C_4H_4ON_2S$.	Found.
N	21.87	21.66



dine¹ was warmed on the steam bath with an aqueous solution containing somewhat more than four times the calculated quantity of potassium hydrosulphide. As soon as the oil disappeared, the hot solution was filtered from slight impurities and acidified with hydrochloric acid. This gave a yellow flocculent precipitate which was recrystallized from water. It was found to be difficultly soluble and it gave a feltlike mass of fine, bright yellow needles, which turned dark and decomposed above 230° without showing a definite melting point.

0.3215 gram substance gave 1.0278 gram BaSO₄.

	Calculated for C ₄ H ₄ N ₂ S ₂ .	I.	Found.	II.
S	44.44	43.79		
N	19.44			19.46

2,6-Dithiouracil was also obtained when 2-ethylmercapto-6-thiopyrimidine was melted in an oil bath at 170° and treated with dry hydrogen chloride. The material quickly solidified in the hot bath. It was then removed and crystallized from water, whereupon the characteristic yellow needles of 2,6-dithiouracil were obtained.

It was also found that when 2-ethylmercapto-6-oxypyrimidine was treated in the same manner 2-thiouracil was formed.²

Action of Chloracetic Acid on 2,6-Dithiouracil: Pyrimidine-



grams of 2,6-dithiouracil were dissolved in hot water and 5 grams of chloracetic acid were added. The solution was evaporated to dryness, the residue taken up in water and

¹ J. Biol. Chem., **3**, 287 (1907).

² See also Wheeler and Liddle: J. Am. Chem. Soc., **30**, 1157 (1908).

evaporated again, the operation being repeated several times or until the yellow color disappeared. The residue was then moderately soluble in alcohol and very difficultly soluble in hot water. It was crystallized from 600 cc. of boiling water, and 2 grams of white powder separated. Boiling with water or even warming with concentrated hydrochloric acid did not desulphurize this substance. When heated it decomposed above 200° .

	Calculated for $C_8H_8O_4N_2S_2$.	Found.
N	10.77	11.14
NEW HAVEN, CONN., September, 1908.		

[Contributions from the Sheffield Laboratory of Yale University.]

CLXV.—RESEARCHES ON PYRIMIDINES:
ON THE FORMATION OF PURINE DERIVATIVES FROM
4-METHYLCYTOSINE.

[FORTY-FIRST PAPER.]

BY CARL O. JOHNS.

It was found by Gabriel and Colman that 4-methyl-6-aminopyrimidine¹ and 2-chlor-4-methyl-6-aminopyrimidine² did not give the expected 5-nitro compounds when nitrated, but instead yielded 6-nitramine derivatives.

When 4-methylcytosine, I.,³ is nitrated in the presence of sulphuric acid, an almost quantitative yield of 4-methyl-5-nitrocytosine, II., is obtained. To determine whether the compound formed was a 6-nitramine or a 5-nitropyrimidine, the nitration product was heated with 30 per cent sulphuric acid in a sealed tube. This treatment gave Behrend's nitromethyluracil,⁴ III., in which the nitro group occupies position 5. This result agrees with previous observations made when pyrimidines containing an amino group in position 6 have been heated with sulphuric acid. When cytosine⁵ was heated with 20 per cent sulphuric acid it gave uracil, and when nitrocytosine⁶ was heated under similar conditions, nitrouracil was formed.

The reduction of 4-methyl-5-nitrocytosine to 2-oxy-4-methyl-5,6-diaminopyrimidine, IV., presented considerable difficulty. This was not unexpected since it was only after many unsuccessful attempts that 2-oxy-5,6-diaminopyrimidine⁷ was obtained by the reduction of 5-nitrocytosine.

An attempt to reduce 4-methyl-5-nitrocytosine with stannous chloride did not give the desired diaminopyrimidine, and when ammonium sulphide was used, 4-methylcytosine

¹ Ber. d. chem. Ges., **34**, 1240 (1901).

² *Ibid.*, **34**, 1241 (1901).

³ *THIS JOURNAL*, **40**, 348 (1908).

⁴ Ann. Chem. (Liebig), **240**, 3 (1887).

⁵ Wheeler and Johnson: *THIS JOURNAL*, **29**, 494 (1903).

⁶ Johnson, Johns, and Heyl: *Ibid.*, **36**, 116 (1906).

⁷ *Ibid.*, **36**, 170 (1906).

was regenerated. The reduction was finally accomplished by the use of aluminium amalgam. Even then prolonged reduction or a temperature above 45° liberated ammonia and regenerated 4-methylcytosine. If the solution which was obtained from the reduction was evaporated on a water bath at 100° a black residue was obtained. The evaporation was therefore carried out under diminished pressure. When the solution had been concentrated to a small volume, stout, flat crystals of the 2-oxy-4-methyl-5,6-diaminopyrimidine separated. These contained one and one-half molecules of water of crystallization. They could be recrystallized from water without undergoing decomposition and then separated in long prisms that contained but one molecule of water. It is probable that the decomposition observed when the solution obtained from the reduction was evaporated was due to the presence of some unstable by-product.

Gabriel and Colman condensed urea¹ and thiourea² with 4-methyl-5,6-diaminopyrimidine and obtained purine derivatives.

The writer has found that 2-oxy-4-methyl-5,6-diaminopyrimidine also condenses with urea and thiourea to give 2,8-dioxy-6-methylpurine, V., and 2-oxy-6-methyl-8-thiopurine, VI. Moreover, formic acid acts on 2-oxy-4-methyl-5,6-diaminopyrimidine and produces a monoformyl derivative. This compound gives a sodium salt which loses water, when heated, and yields 2-oxy-6-methylpurine, VII.

These reactions with urea and formic acid are such as might be expected of an orthodiamine but not of a hydrazine derivative, and they confirm the assumption that 4-methylcytosine nitrates in position 5.

Emil Fischer³ has called attention to the fact that the introduction of oxygen into purine decreases its solubility in water. In accordance with this, 2-oxy-6-methylpurine is easily soluble in hot water while the same purine with oxygen or sulphur in position 8 is almost insoluble.

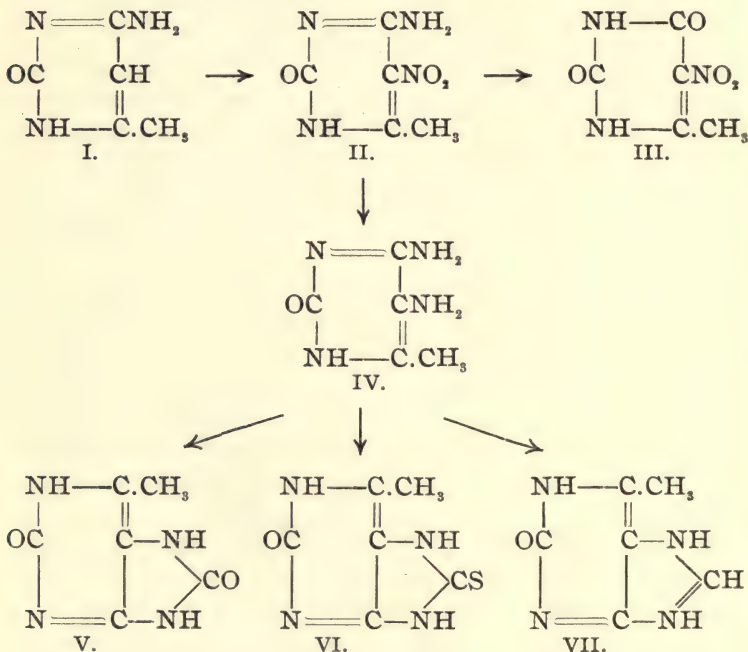
If 2-oxy-5,6-diaminopyrimidine were heated with urea it

¹ Ber. d. chem. Ges., **34**, 1247 (1901).

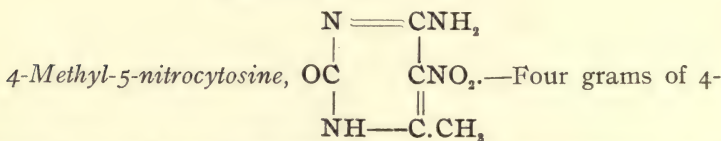
² *Ibid.*, **34**, 1248 (1901).

³ Untersuchungen in der Puringruppe, p. 74.

might be expected to yield 2,8-dioxypurine. This compound is the only one of the three possible dioxypurines which has not been prepared and it has the structure which was at first assigned to xanthine. Later, Emil Fischer showed that xanthine was 2,6-dioxypurine.¹ 6,8-Dioxypurine has been prepared by Fischer and Ach.² The writer has begun work on the synthesis of 2,8-dioxypurine.



EXPERIMENTAL PART.



methylcytosine were dissolved in 11 cc. of concentrated sulphuric acid. Heat was liberated. While the solution was still

¹ Ber. d. chem. Ges., 30, 553 (1897).

² Ibid., 30, 2218 (1897).

warm 11 cc. of nitric acid, density 1.5, were added gradually. The first portions of nitric acid produced considerable heat but no red fumes were evolved. The resulting solution was allowed to stand at room temperature for 10 minutes and was then poured into 100 cc. of cold water. When the acids were neutralized with ammonium hydroxide, 4.8 grams of a yellow precipitate, which corresponds to 90 per cent of the calculated yield, separated. This compound was difficultly soluble in boiling water and crystallized in small pointed prisms. Its slight solubility in water showed that it was not 4-methyl-cytosine. It began to turn brown at 260° and became black at 280° but did not melt. It was soluble in acids and ammonia.

Analysis (Kjeldahl):

	Calculated for $C_5H_6O_3N_4$.	Found.
N	32.94	33.17

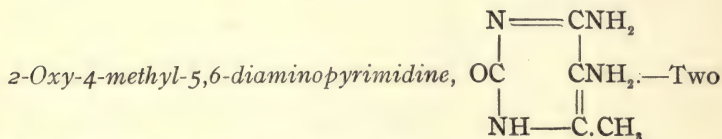
The position of the nitro group was determined as follows: One gram of the nitro compound was dissolved in 20 cc. of 30 per cent sulphuric acid and heated in a sealed tube at 130°–140° for two hours. A deposit of large crystals was obtained when the tube cooled. These were filtered off and the filtrate was analyzed for nitrogen in the form of ammonia by adding sodium hydroxide and distilling into N/10 hydrochloric acid.

N calculated for one NH_2 group, 0.08 gram.

Found, 0.09 gram.

The crystals which were filtered off dissolved readily in boiling water and separated from the cold solution in stout prisms and toothed structures. They possessed all the properties of Behrend's nitromethyluracil, in which the nitro group occupies position 5.

	Calculated for $C_6H_5O_4N_3$.	Found.
N	24.56	24.99



and two-tenths grams of finely pulverized 4-methyl-5-nitro-

cytosine were suspended in 100 cc. of water and reduced vigorously with 1 gram of aluminium amalgam for one-half hour. The temperature was kept below 45° . The aluminium used was in the form of fine drillings. The aluminium hydroxide formed was filtered off by suction and washed with hot water. The filtrate was concentrated under diminished pressure to about 15 cc. Crystals separated during the evaporation. These were redissolved by careful heating and a slight insoluble residue was filtered off. Stout, flat prisms separated on cooling. These became brown above 250° and decomposed slowly at about 280° – 285° without melting. They contained one and one-half molecules of water of crystallization. The yield of pure hydrous crystals was from 50 to 60 per cent of the calculated. Water determinations on crystals obtained from different experiments gave the following results:

- I. 1.6340 gram lost 0.2637 gram of H_2O .
 II. 0.5011 gram lost 0.0805 gram of H_2O .
 III. 1.1859 gram lost 0.1907 gram of H_2O .

	Calculated for $\text{C}_5\text{H}_8\text{ON}_4 \cdot 1\frac{1}{2}\text{H}_2\text{O}$.	I.	Found. II.	III.
H_2O	16.16	16.14	16.06	16.08

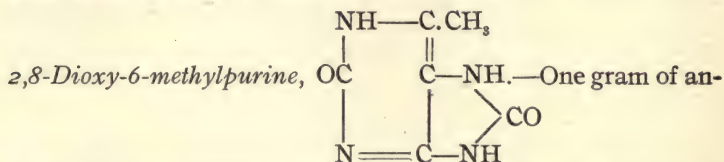
Nitrogen determinations resulted as follows:

	Calculated for $\text{C}_5\text{H}_8\text{ON}_4 \cdot 1\frac{1}{2}\text{H}_2\text{O}$.	Found.
N	33.53	33.61
	Calculated for $\text{C}_5\text{H}_8\text{ON}_4$.	Found.
N	40.00	39.78

When the flat crystals obtained above were recrystallized from water they separated in long prisms that contained but one molecule of water of crystallization. The following analyses were made on different lots of the recrystallized diaminopyrimidine.

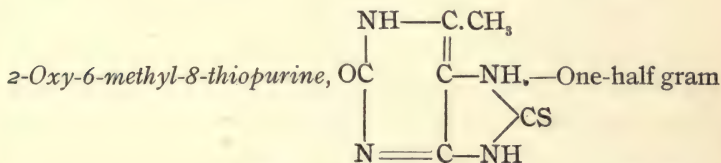
	Calculated for $\text{C}_5\text{H}_8\text{ON}_4 \cdot \text{H}_2\text{O}$.	I.	Found. II.	III.
H_2O	11.39	11.53	11.49	11.42
	Calculated for $\text{C}_5\text{H}_8\text{ON}_4$.		Found.	
N	40.00		40.02	

2-Oxy-4-methyl-5,6-diaminopyrimidine was easily soluble in hot water but it dissolved only slightly in cold water. It did not dissolve in alcohol. The dried crystals were very hygroscopic. Water solutions gave precipitates with mercuric chloride and picric acid. The picrate charred above 240° but did not melt. The best yield was obtained by using fine aluminium drillings and reducing rapidly. If the reduction is prolonged or the temperature raised above 45° , ammonia is liberated and 4-methylcytosine is re-formed.



hydrous 2-oxy-4-methyl-5,6-diaminopyrimidine was intimately mixed with 1 gram of urea by grinding in a mortar. This mixture was heated in an oil bath kept at 170° – 180° for one-half hour. The mass melted and ammonia was evolved. The fusion product was dissolved in boiling water containing a few drops of ammonium hydroxide and the solution was decolorized with animal charcoal. When the filtrate was boiled to drive off ammonia, minute crystals separated. These were almost insoluble in boiling water but dissolved readily in mineral acids and bases. They were insoluble in alcohol or acetic acid. They did not melt at 345° . The yield was 1.1 grams, or 93 per cent of the calculated weight.

	Calculated for $\text{C}_6\text{H}_6\text{O}_2\text{N}_4$.	I.	Found.	II.
N	33.73	33.59		33.81



of 2-oxy-4-methyl-5,6-diaminopyrimidine was ground in a mortar with one gram of thiourea. The mixture was heated in an oil bath kept at 180° – 190° for one hour. It melted and

turned black. Ammonia was evolved. The fusion mass was dissolved in water containing ammonium hydroxide. A clear solution was obtained by using animal charcoal. This solution gave an immediate precipitate when acidified with acetic acid. The compound thus obtained was purified by dissolving in very dilute ammonium hydroxide and reprecipitating with acetic acid. Extremely small crystals were obtained. These were not soluble in alcohol and were almost insoluble in boiling water and boiling acetic acid. They were freely soluble in alkalies and mineral acids. They did not melt at 345° . The yield of the pure purine was 80 per cent of the calculated quantity.

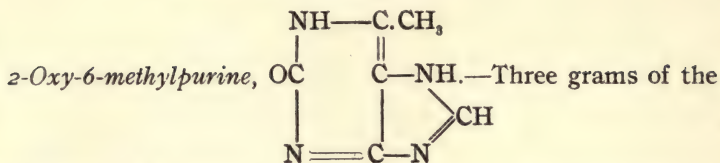
	Calculated for $C_6H_6ON_4S$.	Found.
N	30.77	30.90
S	17.59	17.81

The Monoformyl Derivative of 2-Oxy-4-methyl-5,6-diaminopyrimidine, $C_5H_7ON_4.CHO$.—Four grams of the diaminopyrimidine were dissolved in 4 cc. of formic acid, density 1.2, and the solution was heated on a water bath for one-half hour. The excess of formic acid was evaporated in an open dish and the residue was dissolved in water. When this solution was neutralized with ammonium hydroxide, the monoformyl derivative precipitated. It was moderately soluble in hot water and formed minute crystals when the solution was cooled. It dissolved readily in acetic acid and was slightly soluble in boiling alcohol. The crystals began to turn black at about 325° but did not melt at 345° .

	Calculated for $C_6H_8O_2N_4$	Found.
N	33.33	33.29

Prolonged heating in an oil bath at 240° caused the formyl derivative to darken considerably but it did not lose water to form a purine. When recrystallized from water the heated product exhibited all the properties of the formyl derivative. It was dried at 130° for analysis.

	Calculated for $C_6H_8O_2N_4$.	Found.
N	33.33	33.46



monoformyl derivative of 2-oxy-4-methyl-5,6-diaminopyrimidine were dissolved in an excess of 10 per cent solution of sodium hydroxide. When alcohol was added the sodium salt of the formylpyrimidine separated as a white powder. This salt was dried and heated in an oil bath at 200°. Water came off readily and considerable foaming ensued, leaving a porous crust. This dissolved freely in cold water and did not give a precipitate when the solution was neutralized with acetic acid. The solution was therefore evaporated to dryness and the residue was dissolved in a little hot water. Clusters of slender prisms were obtained when the solution cooled slowly. These turned brown at about 280° and became black above 300° but did not melt at 345°. They were easily soluble in acetic acid and ammonium hydroxide and sparingly soluble in boiling alcohol. A water solution gave a precipitate with mercuric chloride but did not give precipitates with ferric chloride, copper sulphate, or chloroplatinic acid.

	Calculated for C ₆ H ₆ ON ₄ .	I.	Found. II.	III.
N	37.33	37.05	37.10	37.35

NEW HAVEN, CONN.,
November, 1908.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

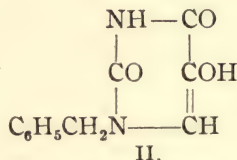
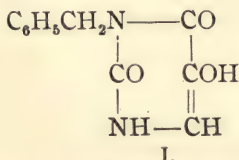
RESEARCHES ON PYRIMIDINES: SYNTHESIS OF 1-METHYL-5-HYDROXYURACIL.

[FORTY-SECOND PAPER.]

BY TREAT B. JOHNSON AND D. BREESE JONES

Received March 19, 1909.

In a previous paper from this laboratory, Johnson and McCollum¹ described a new synthesis of 5-hydroxyuracil (isobarbituric acid). They showed that this pyrimidine is formed quantitatively by hydrolysis of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine with hydrochloric acid. In a recent paper, Johnson and Jones² have shown that nitrogen-alkyl derivatives of this mercaptopyrimidine can be obtained easily and also undergo hydrolysis, giving nitrogen-alkyl derivatives of 5-hydroxyuracil. They prepared by this method 1- and 3-benzyl-5-hydroxyuracils, I., and II.



The object of the work described in this paper was to prepare the nitrogen-methyl derivatives of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine³ and study their behavior on hydrolysis.

5-Hydroxyuracil and nitrogen-alkyl derivatives of this pyrimidine are prepared, according to Behrend's⁴ synthesis, by the reduction of 5-nitrouracil and its alkyl derivatives with tin and hydrochloric acid. The only nitrogen-alkyl derivatives of 5-hydroxyuracil that have been synthesized by this method, are methyl-5-hydroxyuracil (methylisobarbituric acid) and ethyl-5-hydroxyuracil (ethylisobarbituric acid). These pyrimidines are incorrectly represented in Beilstein's Handbuch⁵ as 1-alkyl pyrimidines III, and IV, and were prepared by Lehmann⁶ by reducing methyl- and ethylnitrouracils, to which he assigned, without proof, formulas V, and VI.

¹ *J. Biol. Chem.*, **1**, 437.

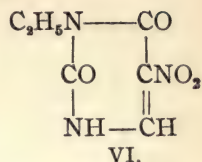
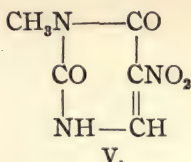
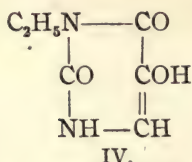
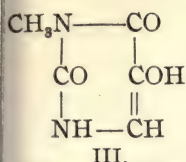
² *Am. Chem. J.*, **40**, 538.

³ *Loc. cit.*

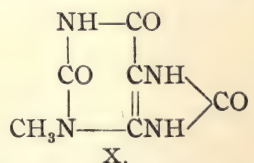
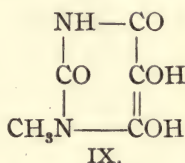
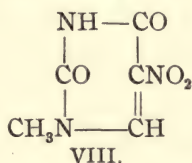
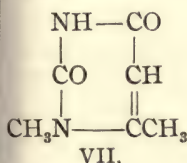
⁴ *Ann.*, **249**, 39; *Ibid.*, **251**, 239.

⁵ *Vol. I*, 1347, 1348.

⁶ *Ann.*, **253**, 77.



The structures of these alkyl nitrouracils, and consequently the corresponding 5-hydroxyuracils of Lehmann's were correctly established by Behrend and Thurm¹ who showed that they are to be represented as 3-alkyl-pyrimidines; for example, 3,4-dimethyluracil (α -dimethyluracil), VII, and nitric acid reacted giving the same nitromethyluracil, VIII, as originally was obtained by Lehmann² by methylation of nitrouracil. Furthermore, the oxidation of Lehmann's methyl-5-hydroxyuracil with bromine water gave a methylisodialuric acid, IX, which condensed with urea, giving 3-methyluric acid (*d*-acid) X.³ Lehmann's



ethylnitrouracil reacted with methyl iodide, giving the same ethylmethylpyrimidine as was obtained from 1-methylnitrouracil and ethyl iodide.⁴

Johnson and Jones⁵ observed that 1-benzyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine is the chief product of the reaction when benzyl chloride acts on 2-ethylmercapto-5-ethoxy-6-oxypyrimidine, XI, in presence of alkali. We now find that methyl iodide reacts with this mercaptopyrimidine, giving a mixture of the corresponding 1 and 3-methylpyrimidines which contains about 70 per cent. of the theoretical yield of 1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine, XII.

2-Ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine, XVI, possessed the unique property of combining with potassium iodide, giving a definite, double compound. We suspected this substance, at first, of being an addition product of methyl iodide and the potassium salt of 1- or 3-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidines. This assumption, however, proved to be incorrect, since the same compound was formed quantitatively by crystallizing 2-ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine from an alcoholic solution of potassium iodide. The analytical determinations agreed with the calculated values for a double compound

¹ *Ann.*, **323**, 160.

² *Loc. cit.*

³ E. Fischer and Ach, *Ber.*, **32**, 2721. Loeben, *Ann.*, **298**, 181. Behrend and Dietrich, *Ann.*, **309**, 260.

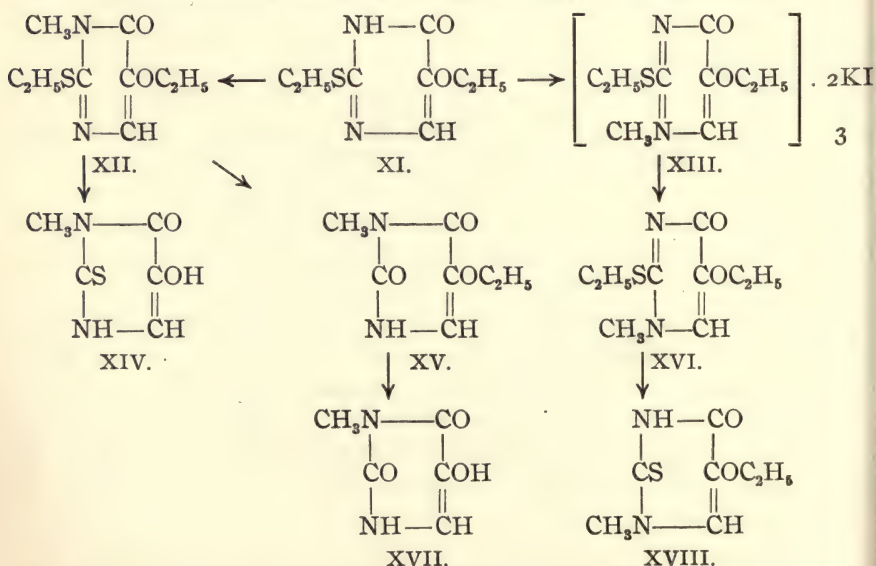
⁴ Behrend and Thurm, *Loc. cit.*

⁵ *Loc. cit.*

containing 3 molecules of the 3-methylpyrimidine and 2 molecules of potassium iodide, XIII.

2-Ethylmercapto-1-methyl-5-ethoxy-6-oxypyrimidine, XII, is converted smoothly into 1-methyl-5-ethoxyuracil, XV, by digestion with hydrochloric acid. When this pyrimidine or the mercaptopyrimidine are heated with strong hydrochloric acid at 120–130°, they are changed practically quantitatively into 1-methyl-5-hydroxyuracil, XVII. Hydrolysis of 2-ethylmercapto-1-methyl-5-ethoxy-6-oxypyrimidine with boiling hydrobromic acid gave a mixture of 1-methyl-2-thio-5-hydroxyuracil, XIV, and 1-methyl-5-ethoxyuracil, XV. The formation of 2-thiopyrimidines from the corresponding mercapto derivatives by hydrolysis with acids has previously been observed by Johnson and Clapp;¹ for example, 2-ethylmercapto-3,5-dimethyl-6-oxypyrimidine gave 2-thio-3,5-dimethyl-6-oxypyrimidine when digested with hydrobromic acid.

The sulphur in 2-thio-1-methyl-5-hydroxy-6-oxypyrimidine, XIV, is very firmly bound. It cannot be removed by digestion with chloracetic acid.² The pyrimidine combines with this acid, giving 1-methyl-2-thioglycollic-acid-5-hydroxy-6-oxypyrimidine which can be digested with concentrated hydrochloric acid without decomposition. When the double compound of 2-ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine and potassium iodide, XIII, was digested with hydrochloric acid, it was converted into 2-thio-3-methyl-5-ethoxy-6-oxypyrimidine, XVIII.

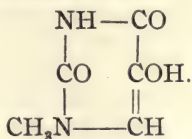


¹ *Jour. Biolog. Chem.*, 5, 57.

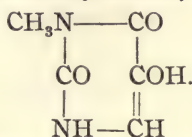
² Wheeler and Liddle, *Am. Chem. J.*, 40, 547.

Summary.

1. Alkylation of 5-nitrouracil with methyl iodide gives chiefly 3-methyl-5-nitrouracil. Reduction of this nitropyrimidine gives 3-methyl-5-aminouracil and 3-methyl-5-hydroxyuracil,



2. Alkylation of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine with methyl iodide gives chiefly 1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine. Hydrolysis of this mercaptopyrimidine with hydrochloric acid at 120–130° gives quantitatively 1-methyl-5-hydroxyuracil,



Experimental Part.

The 2-ethylmercapto-5-ethoxy-6-oxypyrimidine that was used in this work was prepared from ethyl formate and ethyl ethylglycollate according to the directions of Johnson and McCollum.¹ This pyrimidine can be obtained easily in good yield by this method. The yields of pyrimidine obtained in five different condensations are given in the following table:

	Grams $\text{C}_2\text{H}_5\text{OCH}_2\text{COOC}_2\text{H}_5$	Grams HCOOC_2H_5	Grams $\text{NH}_2\text{C}(\text{SC}_2\text{H}_5)\text{NHHBr.}$	Grams of pyrimidine obtained, $\begin{array}{c} \text{NH} - \text{CO} \\ \quad \\ \text{C}_2\text{H}_5\text{SC} \quad \text{COC}_2\text{H}_5 \\ \quad \\ \text{N} - \text{CH} \end{array}$	Per cent. of calculated.
1	113	75	79.5	42.0	48.8
2	102	65	71.8	35.0	45.1
3	109	70	76.7	44.5	53.6
4	76	50	53.5	27.5	47.5
5	76	50	53.5	32.0	55.3

1-Methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine, $\begin{array}{c} \text{CH}_3\text{N} - \text{CO} \\ | \quad | \\ \text{C}_2\text{H}_5\text{S} \quad \text{COC}_2\text{H}_5 \\ || \quad || \\ \text{N} - \text{CH} \end{array}$ — Fifteen

grams of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine¹ and 4.5 grams (1 mol.) of pulverized potassium hydroxide were dissolved in 150 cc. of boiling, absolute alcohol. Fourteen grams of methyl iodide were then added and the mixture warmed, in a water-bath, until it gave no alkaline reaction, when tested with moistened turmeric paper (45 minutes). After cooling, the insoluble potassium iodide (11 grams) was filtered

¹ Loc. cit.

off and the excess of alcohol expelled by evaporation under diminished pressure. This method of procedure was adopted after we had observed, in a preliminary experiment, that the methyl pyrimidine volatilized with alcohol vapors by distillation at ordinary pressure. We obtained a crystalline substance which was extracted several times with an excess of ether and the insoluble part saved (see below). After evaporation of the ether we obtained 11.0 grams of the 1-methylpyrimidine melting at 45–50°. This yield corresponds to about 69 per cent. of the theoretical.

In a second experiment 10.0 grams of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine and 2.85 grams of potassium hydroxide were dissolved in 100 cc. of boiling, absolute alcohol and the solution cooled to 10°. Ten and six-tenths grams of methyl iodide (1.5 mols.) were then added and the solution allowed to stand at 20–5°. Potassium iodide began to separate in one-half an hour and after 3 hours the reaction was complete. The weight of undissolved potassium iodide was 6.25 grams. After evaporation of the alcohol at 40–50° at 47 mm. pressure the residue was then extracted, as usual, with an excess of ether. The yield of 1-methylpyrimidine corresponded to about 71 per cent. of the theoretical. The product insoluble in ether was saved (see below).

The 2-ethylmercapto-1-methylpyrimidine is extremely soluble in ethyl alcohol, benzene and acetone. It crystallized from ether and water in plates melting at 50° to a clear oil. Analysis (Kjeldahl):

Calculated for $C_9H_{14}O_2N_2S$: N 13.08; found, 13.4, 13.20.

The Material Insoluble in Ether.—This substance was extremely soluble in water and difficultly soluble in cold alcohol. It crystallized from a saturated, aqueous solution in characteristic needles arranged in the form of rosettes and from 95 per cent. alcohol in well-developed prisms. It decomposed, when heated slowly, at 177–8° into an oil and a crystalline substance, which did not melt below 250°. The compound contained sulphur and iodine and left an inorganic residue when fused on platinum foil. When some of the compound was dissolved in cold water, and silver nitrate solution added, a gelatinous, white silver salt separated which decomposed, when the solution was warmed, giving yellow silver iodide. The crystalline habit and characteristic properties indicated that we were dealing with a definite compound and not a mixture of a pyrimidine and potassium iodide. Our analytical determinations agreed with the calculated values in a double compound containing 3 molecules of 2-ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine and 2 molecules of potassium iodide, $(C_9H_{14}O_2N_2S)_3 \cdot 2KI$.

Calculated: N, 8.60 ; I, 25.00

Found: N. 8.26, 8.35, 8.40; I, 24.55

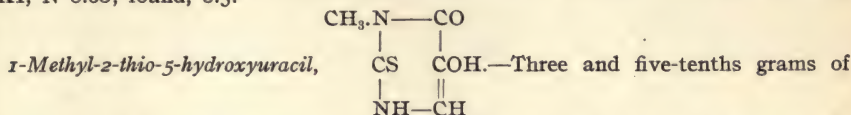
2-Ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine, $C_2H_5SC-CH(CH_3)-N(COCH_2CH_3)-C(=O)-CH_2CH_3$.—Some of the

double compound (above) was heated, in an oil bath, at 175–90° for about 30 minutes. We obtained a crystalline substance, on cooling, which was thoroughly pulverized and digested for a long time with an excess of anhydrous ethyl acetate. After expelling the excess of ethyl acetate at 100°, we obtained a crystalline substance which was extremely soluble in cold water and alcohol. It crystallized from ethyl acetate in clusters of small prisms melting at 140°–51°. They were free from iodine but gave a strong test for sulphur. The compound slowly sublimed when heated at 100°. A mixture of the pyrimidine and 2-ethylmercapto-5-ethoxy-6-oxypyrimidine¹ (melting

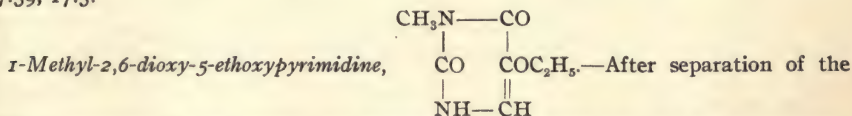
¹ *Loc. cit.*

at 169° melted at 118–25°. Analysis (Kjeldahl): Calculated for $C_9H_{14}O_2N_2S$, N 13.0; found, 13.4.

Crystallization of 2-Ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine from an Alcoholic Solution of Potassium Iodide.—About 0.5 gram of the pyrimidine was dissolved in 25 cc. of hot, absolute alcohol, which had previously been saturated with potassium iodide. On cooling, the double compound, described above, separated in colorless prisms which decomposed at 178°. Analysis (Kjeldahl): Calculated for $(C_9H_{14}O_2N_2S)_2 \cdot 2KI$, N 8.60; found, 8.5.

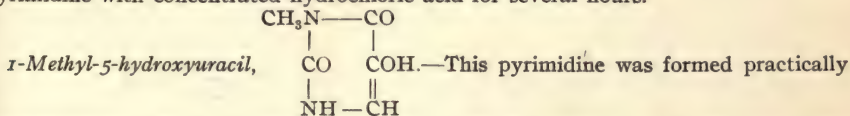


1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine were digested with 20 cc. of hydrobromic acid for about 14 hours. The solution was then evaporated to dryness, when we obtained a crystalline substance which dissolved in boiling water. Upon cooling, about 2.0 grams of slender prisms separated which were extremely insoluble in cold water and boiling alcohol. The material had no definite melting point and gave a strong test for sulphur. It crystallized from hot water without water of crystallization. Analysis (Kjeldahl): Calculated for $C_9H_{14}O_2N_2S$, N 17.7; found, 17.39, 17.5.

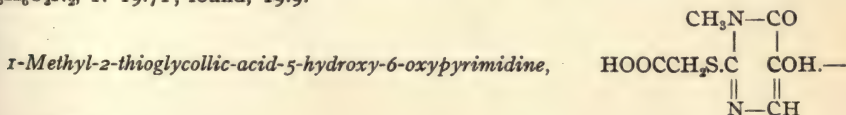


2-thiopyrimidine, in the preceding experiment, the aqueous filtrate was evaporated to dryness. We obtained a crystalline substance which crystallized from hot water in aggregates of short prisms. They turned brown, when heated above 220°, and then melted to an oil at about 240° according to the rate of heating. The compound did not contain sulphur, and reacted with diazobenzene sulphonic acid giving a strong, red color. Analysis (Kjeldahl): Calculated for $C_7H_{10}O_3N_2$, N 16.47; found, 16.7.

This same pyrimidine is obtained smoothly and practically free from 1-methyl-2-thio-5-hydroxyuracil by digestion of 1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine with concentrated hydrochloric acid for several hours.



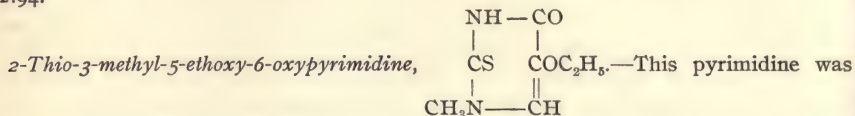
quantitatively when 1-methyl-2,6-dioxy-5-ethoxypyrimidine or 1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine was heated with concentrated hydrochloric acid at 120–30° for 2–3 hours. The pyrimidine is more soluble in water than the isomeric 3-methyl-5-hydroxyuracil.¹ It dissolves readily in boiling water and alcohol and separates from hot aqueous solutions in clusters of radiating prisms which melt at 247° to an oil with slight effervescence. The isomeric pyrimidine decomposes above 260° without melting, with violent effervescence. A mixture of the 1- and 3-methyl-5-hydroxyuracils melted at 217–30° to an oil. Analysis: Calculated for $C_9H_8O_3N_2$, N 19.71; found, 19.9.



¹ *Loc. cit.*

Two grams of chloracetic acid and 1 gram of 1-methyl-2-thio-5-hydroxyuracil were dissolved in boiling water and the solution evaporated to dryness. We obtained a crystalline compound, which separated from hot water in stout prisms, and decomposed at 217° with effervescence. It gave a strong test for sulphur and crystallized from water without water of crystallization. Analysis (Kjeldahl): Calculated for $C_7H_8O_4N_2S$, N 12.96; found, 12.8.

This pyrimidine was extremely stable in presence of hydrochloric acid. Some of the compound was dissolved in a large excess of concentrated acid and the solution evaporated to dryness. The pyrimidine was recovered unaltered and decomposed sharply at 217° . Analysis (Kjeldahl): Calculated for $C_7H_8O_4N_2S$, N 12.96; found, 12.94.



obtained, in small amount, when the double compound of potassium iodide and 2-ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine was digested with hydrochloric acid. After expelling the hydrochloric acid, we obtained a crystalline substance which was washed with alcohol and then crystallized from hot water. It separated in long needles which melted at $210-1^{\circ}$ to an oil, without effervescence. It contained sulphur and gave a violet colored solution by treatment with bromine water and barium hydroxide. Analysis (Kjeldahl): Calculated for $C_7H_{10}O_2N_2S$, N 15.05; found, 15.05.

NEW HAVEN, CONN.

[Contributions from the Sheffield Laboratory of Yale University.]

CLXVII.— RESEARCHES ON PYRIMIDINES:
THE PREPARATION OF 3-METHYL- AND 3-
BENZYLURACIL.

[FORTY-THIRD PAPER.]

BY HENRY L. WHEELER AND TREAT B. JOHNSON.

From a theoretical standpoint a larger number of alkyl compounds may result by alkylating a uracil derivative than can be obtained by a similar treatment of a 2-mercapto-6-oxypyrimidine. With the mercaptopyrimidines only three mono-derivatives should result. With uracil, 4-methyluracil, thymine, or 5-methyluracil, in each case there are ten possible compounds, four mono- and six dialkyl derivatives. This includes oxygen derivatives, but not tautomeric forms. In the case of the 2-amino-6-oxypyrimidines, the guanidine derivatives, the alkylation may be still more complicated.

The work done in this laboratory has therefore been confined almost entirely to the alkylation of mercaptopyrimidines. 2-Ethylmercapto-6-oxypyrimidine¹ and 2-ethylmercapto-5-ethoxy-6-oxypyrimidine² gave with potassium hydroxide and methyl iodide the 1-methyl derivatives in largest quantity, while 2-ethylmercapto-5-methyl-6-oxypyrimidine³ gave a mixture of about equal amounts of the 1- and 3-methylated products. 2-Ethylmercapto-5-ethoxy-6-oxypyrimidine⁴ with benzyl chloride also gave a 1-benzyl derivative as the chief product.

On the other hand 2-ethylmercapto-6-oxypyrimidine⁵ and 2-ethylmercapto-5-methyl-6-oxypyrimidine gave mostly 3-alkyl compounds with benzyl chloride. A similar result was obtained with the former pyrimidine and ethyl chloracetate.⁶

Besides the N isomers there were probably formed, in most of these cases, some 6-oxyalkyl derivatives (oils), the amount

¹ Johnson and Heyl: *THIS JOURNAL*, **37**, 628 (1907).

² Johnson and Jones: *Ibid.*, **40**, 538 (1908).

³ Johnson and Clapp: *J. Biol. Chem.*, **5**, 51 (1908).

⁴ Johnson and Jones: *Loc. cit.*

⁵ Johnson and Derby: *THIS JOURNAL*, **40**, 444 (1908).

⁶ Wheeler and Liddle: *J. Am. Chem. Soc.*, **30**, 1152 (1908).

of 6-oxy derivative being noteworthy in the methylation of 2-anilino-6-oxypyrimidine.¹

These examples show that no regularity is observed in the alkylation of 2-mercapto-6-oxypyrimidines, that analogous salts can give different results with the same halide, and that with different halides the salts may be attacked in different positions. It will also be noticed from the above that the papers so far published have contained accounts only of the results obtained with 2-mercapto-6-oxypyrimidines. It was therefore of interest to study the alkylation of some isomeric 2-oxy-6-mercaptopyrimidines and to examine the effect produced when the mercapto group and the oxygen atom were interchanged.

We now find when 2-oxy-6-methyl-mercaptopyrimidine (V.) is treated with potassium hydroxide, in alcoholic solution, and either methyl iodide or benzyl chloride, that 3-alkyl derivatives result. The amount of isomeric products, if any, formed in this reaction is very small.

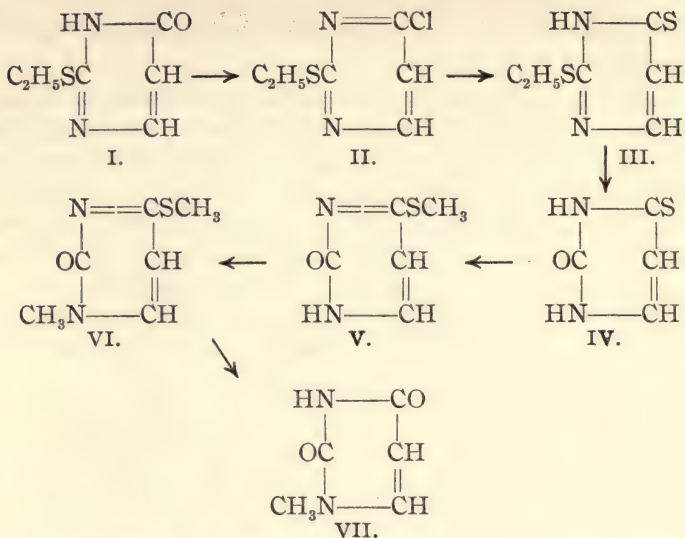
The 6-mercapto derivatives, like the 2-mercapto compounds, on boiling with hydrochloric acid evolve mercaptan and pass smoothly into uracil derivatives. The new 3-methyluracil (VII.) thus obtained now completes the list of the theoretically possible monomethyluracils. It gives no color with diazobenzenesulphonic acid although the isomeric 1-methyluracil gives a red coloration.²

2-Oxy-6-methylmercaptopyrimidine (V.) was prepared by methylating 6-thiouracil (IV.), while the preparation of the latter substance has been described by Wheeler and Liddle.³ The various steps in the synthesis of 3-methyluracil may be represented as follows:

¹ Johnson and Heyl: *THIS JOURNAL*, **38**, 238 (1907).

² Johnson and Clapp: *J. Biol. Chem.*, **5**, 163 (1908)

³ *THIS JOURNAL*, **40**, 547 (1908).



3-Methyluracil dissolves in alkali and is precipitated unaltered by hydrochloric acid.

Müller¹ obtained a 3-methyluracil-4-carboxylic ester by condensing oxalacetic ethyl ester and methylurea. When the sodium salt of this substance was treated with hydrochloric acid he obtained β -methyluramidoacrylic acid, $\text{H}_2\text{N} \text{---} \text{CO} \text{---} \text{N}(\text{CH}_3)\text{CH}=\text{CHCOOH}$. Neither acids nor alkalies changed this substance into 3-methyluracil.

Similar peculiar relations have been observed before in the pyrimidine series. Fischer and Roeder² in their synthesis of uracil obtained an acid which differed from uracil by one molecular proportion of water. It was left undecided whether this substance was uracilic acid (Uracilsäure), $\text{H}_2\text{N} \text{---} \text{CO} \text{---} \text{NHCH}=\text{CHCOOH}$, or oxyhydrouracil,

$\text{HN} \text{---} \text{CO} \text{---} \text{NH} \text{---} \text{CH}_2 \text{---} \text{CHOHCO}$. They did not succeed in converting the substance into uracil.

Johnson and Clapp³ obtained two α -methyl- β -guanidine-acrylic acids. One could be dissolved in dilute alkali and be

¹ J. prakt. Chem., **56**, 498 (1897).

² Ber. d. chem. Ges., **34**, 3760 (1901).

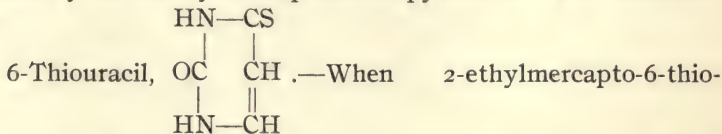
³ THIS JOURNAL, **32**, 130 (1904).

reprecipitated by acids unaltered, with the other this treatment closed the ring and gave 2-amino-5-methyl-6-oxy-pyrimidine. The explanation given for the existence of these two acids was that they represented the *cis* and *trans* modifications.

Such an explanation might also account for the fact that—like Müller's pyrimidines—certain uracil derivatives dissolve in alkali and on precipitating with acids give the corresponding uramidoacrylic acids, while others—such as our 3-methyl-uracil—are precipitated in the form having the closed, uracil ring.

EXPERIMENTAL PART.

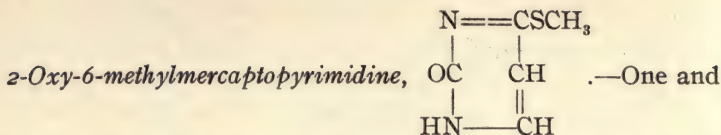
The preparation of 2-ethylmercapto-6-thiopyrimidine from 2-ethylmercapto-6-chloropyrimidine¹ has been described by Wheeler and Liddle.² In the present work instead of employing two and a half times the calculated quantity of potassium hydrosulphide we have taken four times the calculated amount. By this method a yield of over 90 per cent of the calculated quantity of 2-ethylmercapto-6-thiopyrimidine was obtained.



pyrimidine is treated with concentrated hydrochloric acid the pale yellow color of the compound changes to a bright yellow. If water is added the color disappears or becomes much lighter. If this solution is boiled too long the material is completely desulphurized and uracil is obtained. The following procedure, however, gave a yield of over 90 per cent of the calculated amount of 6-thiouracil: Nine and six-tenths grams of 2-ethylmercapto-6-thiopyrimidine were added to a mixture of 50 cc. of concentrated hydrochloric acid and 50 cc. of water. On warming, mercaptan was evolved and solution took place, then 6-thiouracil separated. The acid was evaporated on the steam bath and the residue was crystallized from water.

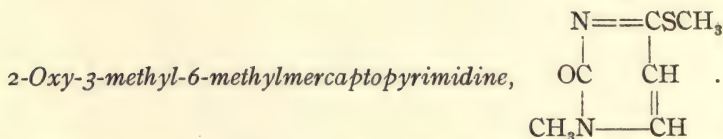
¹ Wheeler and Johnson: THIS JOURNAL, **29**, 496 (1903); **31**, 596 (1904).

² *Ibid.*, **40**, 555 (1908).



one-tenth grams of sodium were dissolved in 25 cc. of methyl alcohol and 6.1 grams of 6-thiouracil were added. The mixture became semisolid owing to the separation of a colorless, difficultly soluble sodium salt. Ten grams of methyl iodide and 25 cc. more methyl alcohol were added. On warming the mixture, solution soon took place and it then gave a neutral reaction. The alcohol was evaporated and the residue was treated with water. Crystalline material separated which, after washing with water and drying, weighed 5 grams, or 73.7 per cent of the calculated. This dissolved easily in hot water and on cooling, long, slender needles or prisms were obtained melting to an oil with no effervescence at 205°.

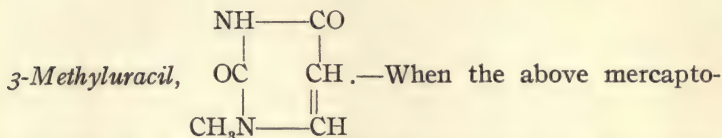
	Calculated for $\text{C}_5\text{H}_6\text{ON}_2\text{S}$.	Found.
N	19.71	19.50



—Four and four-tenths grams of sodium were dissolved in 100 cc. of absolute alcohol and then 10.5 grams of 6-thiouracil were added. On warming a clear solution resulted. The solution was then cooled and 28 grams of methyl iodide were added. A mass of colorless crystals consisting of the sodium salt of 2-oxy-6-methylmercaptopyrimidine separated. On adding 100 cc. more of alcohol and warming for a few hours a clear solution that had a neutral reaction was again obtained. The alcohol was then evaporated off, the final portions in a vacuum. The product was separated from sodium iodide by repeated extractions with chloroform. When about 9.5 grams of material had been extracted it was purified by crystallizing from benzene. It separated in needles which melted at 124° to a clear oil without effervescence.

It was very soluble in cold water, alcohol, chloroform, and boiling ethyl acetate.

	Calculated for $C_6H_8ON_2S$.	Found.
N	17.95	17.76



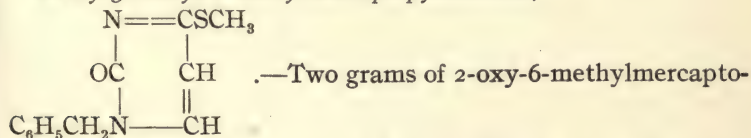
pyrimidine was boiled with strong hydrochloric acid mercaptan was readily given off and on evaporating the acid under diminished pressure colorless prisms were obtained. The crude product melted at 223° – 226° while 1-methyl uracil melts at 174° – 175° .¹

The material was very soluble in water and boiling alcohol. It crystallized from absolute alcohol in rectangular prisms and from hot saturated, aqueous solutions in needles which melted at 232° to an oil without effervescence. It gave no red color with diazobenzenesulphonic acid in presence of sodium hydroxide. With bromine water and barium hydroxide it gave a purple precipitate. 3-Methyluracil is less soluble in cold water than 1-methyluracil.

	Calculated for $C_6H_6O_2N_2$.	Found.
N	22.22	21.90

Some of the above material was dissolved in cold dilute sodium hydroxide and the solution carefully neutralized with dilute hydrochloric acid. The pyrimidine was recovered unaltered and melted at 232° .

2-Oxy-3-benzyl-6-methylmercaptopyrimidine,



pyrimidine and 1.8 grams of benzyl chloride were dissolved in about 30 cc. of alcohol containing one molecular proportion of potassium hydroxide (0.8 gram). There was an immediate

¹ Johnson and Heyl: THIS JOURNAL, **37**, 633 (1907).

reaction when the mixture was heated and potassium chloride separated. The solution was warmed on the steam bath until it gave no alkaline reaction. The potassium chloride was then filtered off and the solution was cooled, whereupon the benzyl derivative separated in prisms melting at 148° – 149° to an oil without effervescence. This melting point was not raised by recrystallizing from alcohol. The alcohol filtrates were evaporated to dryness on the steam bath and the residue was treated with dilute sodium hydroxide to remove any unaltered material. The insoluble portion melted without further purification at 146° – 148° and was practically pure 3-benzyl derivative. The yield of this pyrimidine was 2.9 grams, or 90 per cent of the calculated. No evidence of the formation of an isomeric benzyl derivative was obtained.

	Calculated for $C_{12}H_{12}ON_2S$.	Found.
N	12.06	12.19

When this mercaptobenzylpyrimidine was boiled with hydrochloric acid it gave a quantitative yield of 3-benzyluracil¹ melting at 172° – 173° . A mixture of this compound and a sample of 3-benzyluracil melted at 172° – 173° , while a mixture of the pyrimidine in question and 1-benzyluracil (m. p. 175°) melted at 140° – 145° .

Action of Methyl Iodide on 2-Ethylmercapto-6-oxypyrimidine.
—We have reexamined the action of methyl iodide on the potassium salt of 2-ethylmercapto-6-oxypyrimidine² and we now find that both 1- and 3-methyl derivatives are formed. In the previous work only the 1-methyl derivative was isolated. A mixture of 2-ethylmercapto-6-oxypyrimidine (15.2 grams), potassium hydroxide (5.6 grams), and methyl iodide (18 grams), in 75 cc. of alcohol was warmed on the steam bath until the solution gave a neutral reaction. It was then evaporated to a syrup and a little water was added. This caused the separation of 3.6 grams of 1-methyl-2-ethylmercapto-6-oxypyrimidine which was filtered off. The filtrate was boiled with hydrochloric acid and evaporated to dryness and the

¹ Johnson and Derby: *THIS JOURNAL*, **40**, 444 (1908).

² Johnson and Heyl: *Loc. cit.*

residue was repeatedly extracted with boiling alcohol. The part insoluble in alcohol proved to be uracil. The alcoholic solution was decolorized with animal charcoal and some sulphur dioxide. The alcohol was evaporated and the residue was fractionally crystallized from water. We then obtained the 3-methyluracil melting at 232° and the 1-methyl derivative melting at 174° . Owing to their similar solubility in alcohol, water, and other solvents it is impossible to make even an approximately quantitative separation by this treatment. It seems to us, however, that the 1-methyl derivative is formed in largest quantity. Further work may show that these proportions vary with change of conditions.

NEW HAVEN, CONN.,
April, 1909.

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[Contributions from the Sheffield Laboratory of Yale University.]

CLXVIII.—RESEARCHES ON PYRIMIDINES:
THE PREPARATION OF 1,4-DIMETHYLURACIL AND
OF THE MONOBENZYL DERIVATIVES OF
4-METHYLURACIL.¹

[FORTY-FOURTH PAPER.]

BY HENRY L. WHEELER AND DAVID F. MCFARLAND.

Behrend² has shown, in his work on the methylation of 4-methyluracil with alkali and methyl iodide, that the three products 1,4-dimethyluracil, 3,4-dimethyluracil, and 1,3,4-trimethyluracil, are all formed and have to be dealt with in addition to unaltered material.

List³ found that 2-thio-4-methyluracil (I.) is readily methylated and that the alkyl group unites with the sulphur, producing 2-methylmercapto-4-methyl-6-oxypyrimidine (II.). List did not determine what was formed on further alkylation.

¹ Part of a Thesis presented by David F. McFarland for the Degree of Ph.D., Yale, 1909.

² Behrend and Dietrich: *Ann. Chem. (Liebig)*, **309**, 265 (1899). Behrend and Meyer: *Ber. d. chem. Ges.*, **33**, 624 (1900). Behrend and Thurn: *Ann. Chem. (Liebig)*, **323**, 160 (1902).

³ *Ann. Chem. (Liebig)*, **236**, 12 (1886).

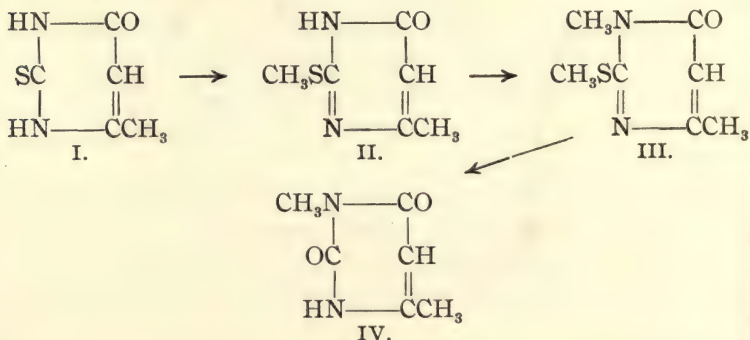
In previous papers from this laboratory it has been shown that 2-mercapto-6-oxypyrimidines usually give a mixture of the 1- and 3-alkyl derivatives on further alkylation.¹

We will now show that the potassium salt of List's 2-methylmercapto-4-methyl-6-oxypyrimidine, in alcoholic solution, alkylates almost entirely in the 1-position with methyl iodide and that 1,4-dimethyl-2-methylmercapto-6-oxypyrimidine (III.) is formed. There are indications also, in this reaction, of the formation of 2-methylmercapto-4-methyl-6-methoxypyrimidine in small amount.

Since the alkylmercaptopyrimidines easily evolve mercaptan and form the corresponding uracil derivatives on boiling with hydrochloric acid, this method is the best (*Darstellung*) for the preparation of 1,4-dimethyluracil (IV.).

By condensing acetoacetic ethyl ester with thiourea in alcoholic solution and in the presence of two molecular proportions of sodium ethylate, a quantitative yield of List's 2-thio-4-methyluracil (I.) may be obtained. The condensation also takes place in alkaline aqueous solution but the yield is not as good. Even this process is far superior to the original methods.²

The steps in the synthesis of 1,4-dimethyluracil may be represented as follows:



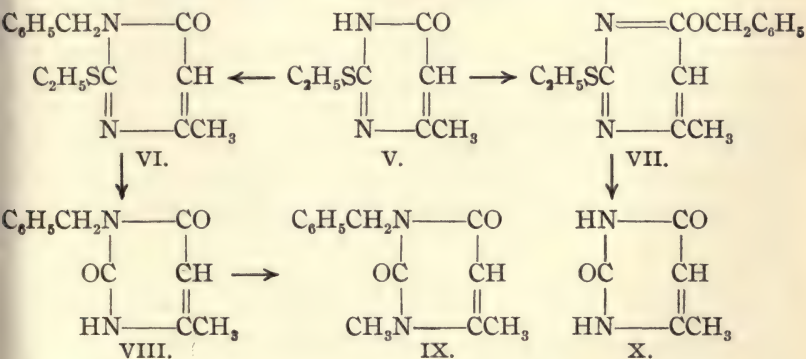
Acetoacetic ethyl ester condenses with ethylpseudothiourea,

¹ For a list of these cases see our forty-third paper on pyrimidines, *THIS JOURNAL*, **42**, (1909).

² Nencki and Sieber: *J. prakt. Chem.*, [2] **25**, 72 (1882). List: *Loc. cit.*

$\text{H}_2\text{N} - \text{C}(\text{SC}_2\text{H}_5)\text{NH}$, in alkaline aqueous solution more smoothly and gives a larger yield (over 80 per cent) of mercaptopyrimidine than in the case of the corresponding condensations of the sodium salts of either ethyl formylacetate or ethyl formylpropionate.

When 2-ethylmercapto-4-methyl-6-oxypyrimidine (V.), prepared in this manner, was treated with sodium hydroxide and benzyl chloride, a mixture of 1-benzyl-2-ethylmercapto-4-methyl-6-oxypyrimidine (VI.) and 2-ethylmercapto-4-methyl-6-benzoyloxypyrimidine (VII.) was obtained. This mixture, which was obtained as an oil insoluble in alkali, could not be separated by distillation under reduced pressure. When it was boiled with hydrochloric acid mercaptan escaped and a new benzyl-4-methyluracil, melting at 194° , along with 4-methyluracil, was obtained.



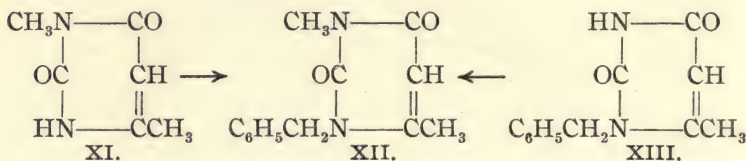
Hagen¹ described a benzyl-4-methyluracil melting at 233° which he obtained in very small amount—the quantity being only sufficient for analysis—by heating the dry potassium salt of 4-methyluracil at a high temperature with benzyl chloride. This substance is given in Beilstein's *Handbuch*² as 1-benzyl-4-methyluracil (VIII.).

We now find that this is incorrect and that the compound is 3-benzyl-4-methyluracil (XIII.). The proof of the structure of these compounds was obtained as follows: 1,4-Dimethyl-

¹ Ann. Chem. (Liebig), **244**, 9 (1888).

² [3] **2**, 529.

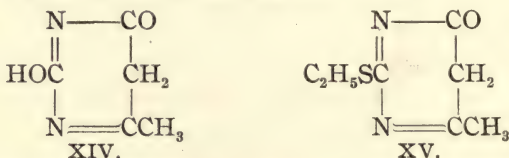
uracil (XI.) was treated with potassium hydroxide and benzyl chloride in alcoholic solution. This gave 1,4-dimethyl-3-benzyluracil (XII.), melting at 85° – 86° . Hagen's benzylmethyluracil, which we find is easily obtained, along with the isomer melting at 194° , when 4-methyluracil, potassium hydroxide and benzyl chloride are warmed in alcoholic solution, was then methylated; the same dimethylbenzyluracil melting at 85° – 86° was thereby obtained.



When the new 1-benzyl-4-methyluracil (VIII.) was methylated it gave the isomeric 1-benzyl-3,4-dimethyluracil (IX.), melting at 164° .

The possibility of an alkylation taking place in the 5-position in the case of pyrimidines derived from acetoacetic ester had to be considered, at this point, before the above results could be taken as proof of the structures assigned to the benzyl compounds in question. Barbituric acid or 2,4,6-trioxy-pyrimidine alkylates under the same conditions in the 5-position.¹

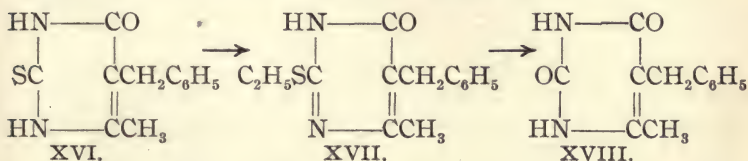
From the analogy which exists between acetoacetic ester and malonic ester it might be expected that 4-methyluracil or 2-ethylmercapto-4-methyl-6-oxypyrimidine might react in the tautomeric forms represented by formulas (XIV.) and (XV.) and yield 5-benzyl derivatives.



In order to prepare 4-methyl-5-benzyluracil (XVIII.) it was necessary to condense benzylacetoacetic ester with a urea

¹ Conrad and Gutzeit: *Ber. d. chem. Ges.*, **14**, 1643 (1881); **15**, 2846 (1882). Fischer and Diltthey: *Ann. Chem. (Liebig)*, **333**, 338 (1904).

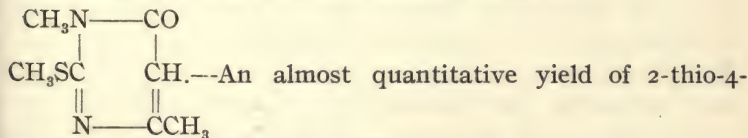
derivative. This ester proved to be one of those β -ketone esters which failed to condense satisfactorily by the general method with the pseudothiourreas in aqueous solution. We find, however, that it condenses in alcoholic solution with thiourea in the presence of sodium ethylate, giving the sodium salt of 2-thio-4-methyl-5-benzyluracil (XVI.). In order to desulphurize this it was found best to convert it into 2-ethyl mercapto-4-methyl-5-benzyl-6-oxypyrimidine (XVII.) which, on boiling with hydrochloric acid, easily gave the desired 4-methyl-5-benzyluracil (XVIII.) melting at 249° – 250° .



Since this compound, melting at 249° – 250° , is different from either of the above benzylmethyluracils it follows that in the alkylation of the pyrimidines derived from acetoacetic ester, under the conditions stated, the benzyl group does not enter the 5-position, and that the various benzyl compounds are correctly represented by the formulas given above. The isomeric benzyloxypyrimidines would not be stable when boiled with hydrochloric acid and are therefore excluded. This otherwise completes the list and settles the structure of the monobenzyl derivatives of 4-methyluracil.

EXPERIMENTAL PART.

1,4-Dimethyl-2-methylmercapto-6-oxypyrimidine,



methyluracil was usually obtained when 30 grams of acetoacetic ester and two molecular quantities of sodium ethylate, made by dissolving 10.6 grams of sodium in 200 cc. of absolute alcohol, were warmed for half an hour with 17.5 grams of thio-

urea. On evaporating the alcohol on the steam bath, which appears to render the condensation more nearly complete, the sodium salt of 2-thio-4-methyluracil remained. This salt easily dissolved in water. On addition of acetic acid to the solution, 2-thio-4-methyluracil was precipitated. The precipitate is apt to carry down with it some of the sodium salt, and it was found advisable to warm it, after filtering, with water acidified with acetic acid. Then on washing with water it is obtained pure and free from sodium.

When 2-thio-4-methyluracil is treated with two molecular proportions of potassium hydroxide and methyl iodide a considerable quantity of 2-methylmercapto-4-methyl-6-oxypyrimidine is obtained. In order to produce a satisfactory alkylation on the nitrogen it is necessary to use a greater excess of alkali and methyl iodide. Potassium hydroxide gives better results in nitrogen alkylation than sodium hydroxide.

Thirty grams of 2-thio-4-methyl-6-oxypyrimidine were dissolved with 35 grams of potassium hydroxide in 150 cc. of absolute alcohol. The potassium salt formed was much more soluble than the free pyrimidine. After cooling the solution, 94 grams of methyl iodide, an excess of 4 grams over that calculated for 3 molecular quantities, were gradually added and the mixture was allowed to stand two days. At the end of that time, about 6 hours' gentle heating on the steam bath was required to complete the reaction so that the solution gave no alkaline test with moist turmeric paper. The alcohol was then evaporated, under diminished pressure, and the solid residue was treated with dilute sodium hydroxide. The undissolved portion was filtered and washed with a little water. Twenty-five and one-tenth grams of 1,4-dimethyl-2-methylmercapto-6-oxypyrimidine melting at 85° – 90° were obtained. An additional 2.3 grams were recovered by shaking the alkaline mother liquor with ether, making the total yield of the compound 27.4 grams, or 76.4 per cent. of the calculated yield. From the alkaline solution 4.5 grams of 2-methylmercapto-4-methyl-6-oxypyrimidine, formed by incomplete methylation, were obtained on acidifying. Al-

lowing for this, the yield of 1,4-dimethyl-2-methylmercapto-6-oxypyrimidine becomes 91.2 per cent of the calculated.

In another experiment where only two molecular proportions of alkali and of methyl iodide were used with 27 grams of 2-thio-4-methyluracil, the amount of intermediate 2-methylmercapto-4-methyl-6-oxypyrimidine was largely increased, 8 grams of it being formed, with a corresponding decrease of dimethylmercapto compound. This shows that a large excess of alkali and of methyl iodide is necessary in order to completely methylate 2-thiouracil.

A small quantity of oily substance, with a pungent odor resembling that of parsnips, coated the material insoluble in alkali. It is probable that this oil is a 6-methoxy derivative but not enough was obtained to permit of its identification. When the material insoluble in alkali was crystallized from water it gave needles which melted sharply at 94° and the results on analysis agreed with those calculated for 1,4-dimethyl-2-methylmercapto-6-oxypyrimidine.

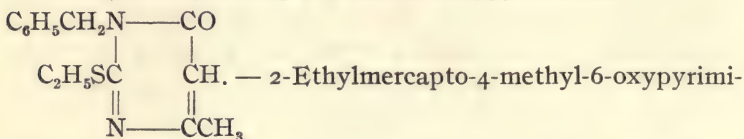
	Calculated for $C_7H_{10}ON_2S$.	Found.
N	16.22	16.47

The substance is readily soluble in alcohol and boiling water, crystallizing from aqueous solutions in silky needles. It is extremely soluble in ether, chloroform and benzene, and rather difficultly soluble in petroleum ether. It sublimes readily at the temperature of the steam bath, condensing again in fine silky needles. It is easily volatile with steam, and solutions containing it cannot be evaporated on the steam bath without loss.

Action of Hydrochloric Acid: 1,4-Dimethyluracil.—The above 1,4-dimethyl-2-methylmercaptopyrimidine was boiled for one hour with strong hydrochloric acid under a reflux condenser to prevent loss of the volatile compound. By this treatment it was quantitatively converted into Behrend's β -dimethyluracil (1,4-dimethyluracil). One recrystallization from hot water gave material melting sharply to a clear oil at 260° – 261° .

No trace of Behrend's isomeric α -dimethyluracil (3,4-dimethyluracil) melting at 220° was found in any of the mother liquors from the above. It is reasonably certain, therefore, that the corresponding 2-methylmercapto-3,4-dimethyl-6-oxypyrimidine was not formed in appreciable quantities.

1-Benzyl-2-ethylmercapto-4-methyl-6-oxypyrimidine,



dine was prepared by condensing acetoacetic ethyl ester with ethyl pseudothiurea in aqueous, alkaline solution; from 54.5 grams of acetoacetic ester a yield of 58.5 grams of crude mercapto compound was obtained, or 81.5 per cent of the calculated.

Twenty grams of this compound were added to a solution of 2.95 grams of sodium in 60 cc. of alcohol. After complete solution had been effected 16.2 grams of benzyl chloride were added and the mixture was heated on the water bath until no further alkaline reaction could be obtained with moist turmeric paper. This required about four hours. The alcohol was then evaporated under diminished pressure and the residue treated with 20 cc. of water and 10 cc. of dilute sodium hydroxide. A heavy oil remained undissolved. This was shaken out with ether; the ether solution was washed with water to remove alcohol, dried over solid potassium hydroxide, and filtered into a weighed flask. After evaporating the ether, 20.7 grams of oil remained, or 68 per cent of the calculated monobenzyl derivative. From the above alkaline solution 9 grams of unaltered substances and from the oil 6 grams of low-boiling material were obtained. Allowing for these weights, the yield of monobenzyl derivative is 87.5 per cent.

The oil was distilled at 22 mm. pressure and after about six grams of low-boiling oil (benzyl chloride?) had distilled over, the temperature rose to 224° and a little over 10 grams of material distilled between this and 236° . The greater part boiled near 227° . The temperature rose slowly, toward

the last to 260° , where the distillation was stopped. The fractions obtained were only slightly colored. None of them gave any solid even when cooled to -15° . Analyses were made of two separate fractions, one (A) boiling at 227° – 228° , and the other (B) at 228° – 260° . Both gave excellent results for a monobenzyl derivative of 2-ethylmercapto-4-methyl-6-oxypyrimidine.

	Calculated for $C_{14}H_{16}ON_2S$.	A.	Found.	B.
N	10.77	10.63		10.62

Action of Hydrochloric Acid: 1-Benzyl-4-methyluracil.—Two grams of the above fraction B were boiled for two hours with 15 cc. of concentrated hydrochloric acid, during which time mercaptan was evolved. The solution was evaporated to dryness, a solid residue weighing 1.3 grams, which nearly all dissolved in boiling water remaining. After filtering off the small amount of gummy residue which did not dissolve, a crystalline mass separated on cooling. It dissolved in boiling alcohol, and, on cooling gave colorless, rounded, lozenge-shaped crystals melting to a clear oil at 194° . Analysis showed this to be a monobenzyl-4-methyluracil.

	Calculated for $C_{12}H_{12}O_2N_2$.	Found.
N	12.96	12.93

The compound dissolves easily in cold chloroform, moderately in hot alcohol, and rather difficultly in hot water. The crystals from alcohol are characteristic.

By evaporation of the aqueous mother liquor from the above compound, material was obtained which crystallized in clusters of fine needles. It had no sharp melting point but decomposed at 270° – 300° . Analyses of this material gave results which agreed with those calculated for 4-methyluracil. When it was mixed with pure 4-methyluracil, the decomposition point was not lowered. From the two grams of oil hydrolyzed there were obtained about 0.3 gram of 1-benzyl-4-methyluracil and 0.6 gram of 4-methyluracil. This result indicates that the fraction of oil boiling at 228° – 260° consisted about

one-third of 1-benzyl-2-ethylmercapto-4-methyl-6-oxypyrimidine and two-thirds of the isomeric 2-ethylmercapto-4-methyl-6-benzylloxypyrimidine.

A similar hydrolysis of fraction A of the oil yielded approximately equal proportions of 4-methyluracil and 1-benzyl-4-methyluracil, so that this fraction consisted of a corresponding mixture of the mercaptobenzyl compounds. Repeated fractional crystallization of all the residues from this experiment failed to give any other substance besides the two described. No trace of the monobenzyl-4-methyluracil described by Hagen¹ was found, although a painstaking search was made for it.

Action of Benzyl Chloride upon 4-Methyluracil: 3-Benzyl-4-methyluracil.—The 4-methyluracil for this experiment was made by boiling 2-ethylmercapto-4-methyl-6-oxypyrimidine with strong hydrochloric acid until mercaptan ceased to be evolved. It was purified by crystallization from water.

Five and a half grams of 4-methyluracil were heated with 2.44 grams of potassium hydroxide in 50 cc. of absolute alcohol. Complete solution did not take place until a further addition of 50 cc. of alcohol and 28 cc. of water had been made. Six grams of benzyl chloride, or one-half gram excess over the calculated, was then added and the mixture heated for three hours on the steam bath or until no alkaline reaction was obtained.

On evaporating the alcohol, a partially solidified mass remained. Part of this dissolved when warmed with dilute sodium hydroxide. The insoluble part formed a resinous semisolid on cooling; this gum could not be induced to crystallize.

From the alkaline solution acetic acid precipitated a mixture. This was boiled with about 50 cc. of alcohol. The portion which did not dissolve proved to be chiefly 4-methyluracil. On cooling the alcoholic solution, pearly, iridescent, diamond-shaped plates separated which melted about 220°–235°, at least 30° higher than 1-benzyl-4-methyluracil. Three crystallizations from alcohol raised the melting point to 233°–

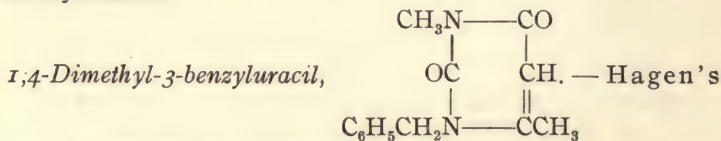
¹ *Loc. cit.*

235°. It therefore agreed with that given by Hagen for his benzyl-4-methyluracil. The compound is very difficultly soluble in hot alcohol and still more difficultly in boiling water. It is almost insoluble in cold chloroform. An analysis of the substance melting at 233°–235° gave results agreeing with those calculated for monobenzyl-4-methyluracil.

	Calculated for $C_{12}H_{12}O_2N_2$.	Found.
N	12.96	13.18

The alcoholic mother liquors from this were evaporated to dryness. The remaining material was then shaken with chloroform. The insoluble part proved to be almost pure 3-benzyl-4-methyluracil (Hagen's compound). The chloroform solution was evaporated to dryness and the residue was crystallized from alcohol, whereupon the isomeric 1-benzyl-4-methyluracil was obtained.

A second benzylation of 4-methyluracil, with 7 grams of the pyrimidine and two molecular proportions of potassium hydroxide (6.22 grams) and of benzyl chloride (14.5 grams) in 115 cc. of alcohol and 35 cc. of water, gave 3.6 grams of gum, insoluble in alkali, 2 grams of unaltered 4-methyluracil, and about 2 grams each of the isomeric nitrogen benzyl-4-methyluracils.



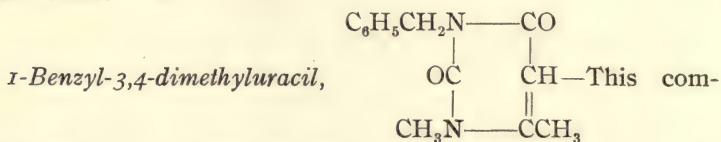
benzyl-4-methyluracil melting at 233° (1.6 grams) was dissolved in 90 cc. of methyl alcohol with three molecular proportions of potassium hydroxide and warmed for three hours and a half with methyl iodide (3.25 grams). The alcohol was then evaporated and the residue was stirred with dilute sodium hydroxide. This left 1.8 grams of oil which on cooling solidified. It was dissolved in ether and the clear, filtered solution was allowed to evaporate slowly in a tall test tube. Beautiful, clear, transparent, prismatic tables were then obtained which melted sharply at 85°–86°. When these

were mixed with 1,4-dimethyl-3-benzyluracil prepared by benzylating 1,4-dimethyluracil the melting point was not lowered. The two preparations agreed in all respects and are identical.

The preparation of this compound from 1,4-dimethyluracil was as follows: Two and eighty-five hundredths grams of 1,4-dimethyluracil and one molecular quantity of potassium hydroxide were dissolved in 120 cc. of 95 per cent alcohol. One molecular portion of benzyl chloride was added and the mixture was heated on the steam bath until a neutral reaction was obtained. A considerable amount of potassium chloride which separated was filtered off and the alcohol was evaporated, a partially solid mass remaining. A portion of this dissolved when treated with sodium hydroxide, leaving 2.1 grams of oil, which finally solidified. When crystallized from ether as described above it melted sharply at 85°-86° and the analytical results were as follows:

	Calculated for $C_{18}H_{14}O_2N_2$.	I.	Found. II.
N	12.17	12.41	12.22

This substance was found to be extremely soluble in alcohol and benzene, much less so in ether, and only slightly in petroleum ether.



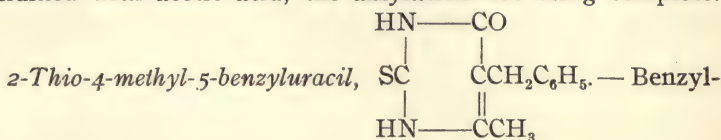
pound, isomeric with the above, was produced when 1.45 grams of 1-benzyl-4-methyluracil melting at 194° was warmed for about four hours with molecular proportions of potassium hydroxide and methyl iodide in 50 cc. of 95 per cent alcohol. The potassium iodide which separated during the reaction was filtered off and the alcohol evaporated to dryness. The residue was treated with dilute sodium hydroxide, washed with water, and dried. It weighed 1.2 grams, or 76 per cent of the calculated. When crystallized from alcohol, beautiful,

long, colorless prisms melting at 164° to a clear oil, were obtained.

An analysis gave results agreeing with the calculated for 1-benzyl-3,4-dimethyl uracil.

	Calculated for $C_{13}H_{14}O_2N_2$.	I.	Found.	II.
N	12.17	12.43		12.32

The alkaline solution above gave 1,4-dimethyluracil when acidified with acetic acid, the alkylation not being complete.



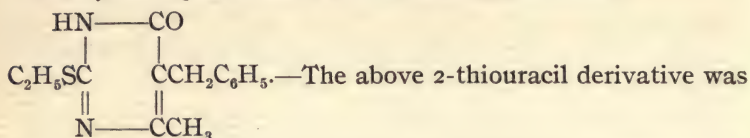
acetoacetic ethyl ester was prepared by the action of benzyl chloride upon the sodium salt of acetoacetic ester, according to the method of Ehrlich.¹ The portion boiling at 194° – 204° at 40 mm. pressure was used in the following work, part of which was done by Mr. McKay S. Howard:

Ten grams of benzylacetoacetic ester and 4 grams of thiourea were added to a solution of sodium ethylate made by dissolving three grams of sodium in 75 cc. of absolute alcohol. The mixture was heated on the steam bath for four hours. The alcohol was then evaporated and the residue was dissolved in water. On the addition of dilute acetic acid 2-thio-4-methyl-5-benzyl-6-oxypyrimidine was precipitated. The yield was 7.4 grams, or 70 per cent of the calculated. The substance was very difficultly soluble in water but more easily in alcohol, from which it crystallized in colorless, leafy plates or scales. After two recrystallizations it melted to a clear oil at 257° – 258° .

	Calculated for $C_{12}H_{12}ON_2S$.	I.	Found.	II.
N	12.07	12.12		12.13

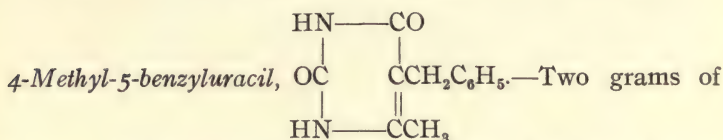
In another experiment, 20 grams of benzylacetoacetic ester gave 13.1 grams of the condensation product, or 62.4 per cent of the calculated.

¹ Ann. Chem. (Liebig), **187**, 12 (1875).

2-Ethylmercapto-4-methyl-5-benzyl-6-oxy pyrimidine,

dissolved in alcohol containing one molecular proportion of sodium ethylate and then allowed to digest with a slight excess of ethyl bromide until the solution was neutral. The product, which was almost insoluble in water, and soluble only with difficulty in cold alcohol, formed fine, prismatic needles melting sharply at 166°.

	Calculated for $\text{C}_{14}\text{H}_{16}\text{ON}_2\text{S}$.	I.	Found.
N	10.77	11.00	10.56



the above mercapto compound were allowed to digest for 24 hours on the steam bath with 50 cc. of concentrated hydrochloric acid. Mercaptan escaped, and, on cooling, 1.6 grams of 4-methyl-5-benzyluracil, or 96 per cent of the calculated, separated. The substance was recrystallized from water and alcohol. It gave diamond-shaped plates melting to a clear oil at 249°–250°.

	Calculated for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_2$.	Found.
N	12.96	13.06

2-Benzylmercapto-4-methyl-5-benzyl-6-oxy pyrimidine.—This was prepared by benzylating 2-thio-4-methyl-5-benzyluracil with molecular quantities of benzyl chloride and sodium ethylate in alcoholic solution. It is nearly insoluble in water. From alcohol it separates in matted masses of long, colorless needles and it melts to a clear oil at 194°.

	Calculated for $\text{C}_{19}\text{H}_{18}\text{ON}_2\text{S}$.	I.	Found.
N	8.69	8.58	8.75

This benzylmercapto compound proved to be very stable when boiled with hydrochloric acid. It was not desulphurized when given the same treatment as that in the case of the corresponding ethylmercapto derivative. When boiled with hydrobromic acid it was finally desulphurized and 4-methyl-5-benzyluracil was obtained. In view of this behavior it is therefore not a matter of indifference what mercapto derivative is chosen for these desulphurizations.

NEW HAVEN, CONN.,
May, 1909.

[Reprinted from The American Chemical Journal,
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[Contributions from the Sheffield Laboratory of Yale University.]

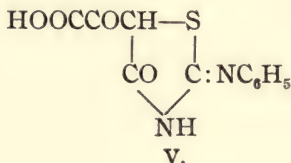
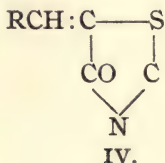
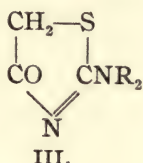
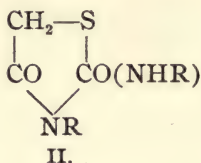
CLXIX.—RESEARCHES ON PYRIMIDINES:
SULPHUR DERIVATIVES OF 5-HYDROXYURACIL:
PREPARATION OF 5-BENZYL MERCAPTOURACIL
AND 5-BENZYL MERCAPTOCYTOSINE.

[FORTY-FIFTH PAPER.]

BY TREAT B. JOHNSON AND HERBERT H. GUEST.

Several investigators have shown that the methylene hydrogens of cyclic compounds which contain the $\text{—S—CH}_2\text{—CO—}$

grouping—rhodanic acids¹ (I) and pseudothiohydantoin² (II) and (III)—react with aldehydes, in presence of alkali, giving unsaturated condensation products (IV). It has also



been shown that the methylene group of arylpseudothiohydantoin is capable of condensing with diethyl oxalate in presence of sodium ethylate. Wheeler and Jamison,³ for example, prepared in this manner phenylpseudothiohydantoinglyoxylic acid (V), from stable phenylpseudothiohydantoin. Loven⁴ examined the behavior of the methylene groups in thiodiglycollic acid towards benzaldehyde and obtained the sulphide of α -mercaptocinnamic acid, $(\text{C}_6\text{H}_5\text{CH:CCOOH})_2\text{S}$, but no attempts, so far as the writer is aware,⁵ have been made to condense ethyl formate or diethyl oxalate with any acyclic compound containing the grouping $\text{—S—CH}_2\text{—CO—}$.

A search of the literature⁶ reveals the fact that no α - or

¹ Nencki: Ber. d. chem. Ges., **17**, 2278 (1884). Giesberg and Bondzynski: *Ibid.*, **19**, 113 (1886). Bondzynski: Monats. Chem., **8**, 349 (1887). Zipser: *Ibid.*, **23**, 958; Centralb., **1903**, I, 283. Andreasch and Zipser: Monats. Chem., **24**, 499; **25**, 159; **26**, 1191; Chem. Ztg., **26**, 54, 623. Stuchetz: Monats. Chem., **26**, 1209. Andreasch: *Ibid.*, **27**, 1211. Wagner: *Ibid.*, **27**, 1223. Bargellini: Atti. Accad. Lincei, [5] **15**, I, 35, 181; Centralb., **1906**, I, 1436, 1438; Gazz. Chim. Ital., **36**, II, 129.

² Andreasch: Monats. Chem., **8**, 407; **10**, 73, 75; Ber. d. chem. Ges., **31**, 138; Centralb., **1899**, II, 804. Wheeler and Jamieson: J. Am. Chem. Soc., **25**, 366 (1903).

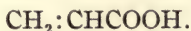
³ Loc. cit.

⁴ Ber. d. chem. Ges., **18**, 3243 (1885).

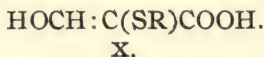
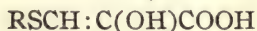
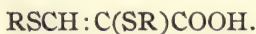
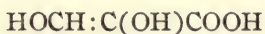
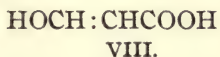
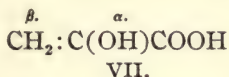
⁵ The writer has signified in a previous paper (THIS JOURNAL, **31**, 290) his intention of condensing diethyl oxalate with diethyl thiodiglycolate.

⁶ Beilstein's Handbuch, Vol. I.

β -mercapto derivatives of acrylic acid (VI), corresponding to α -hydroxy- (VII), β -hydroxy- (VIII), and α,β -dihydroxyacrylic acids (IX), have been described.



VI.



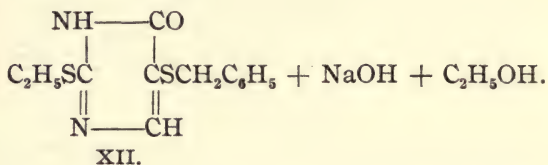
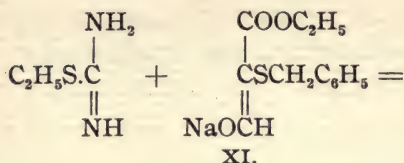
It was, therefore, of especial interest to determine whether ethyl formate would condense with a thioether of ethyl thioglycollate, $\text{HSCH}_2\text{COOC}_2\text{H}_5$, giving an α -mercapto derivative of β -hydroxyacrylic acid (X).

We prepared, for our experiments, ethyl benzylthioglycollate¹ and now find that ethyl formate condenses smoothly with this ester, in presence of metallic sodium, giving ethyl α -benzylmercapto- β -hydroxyacrylate (XIII). We have also condensed ethyl formate with ethyl benzoylthioglycollate,² $\text{C}_6\text{H}_5\text{COSCH}_2\text{COOC}_2\text{H}_5$, under the same conditions, but have reserved the description of this work for publication in another paper.

The sodium salt of ethyl α -benzylmercapto- β -hydroxyacrylate (XI) condensed smoothly with pseudoethylthiourea, in an aqueous solution, giving 2-ethylmercapto-5-benzylmercapto-6-oxypyrimidine (XII). This new condensation is represented by the following equation:

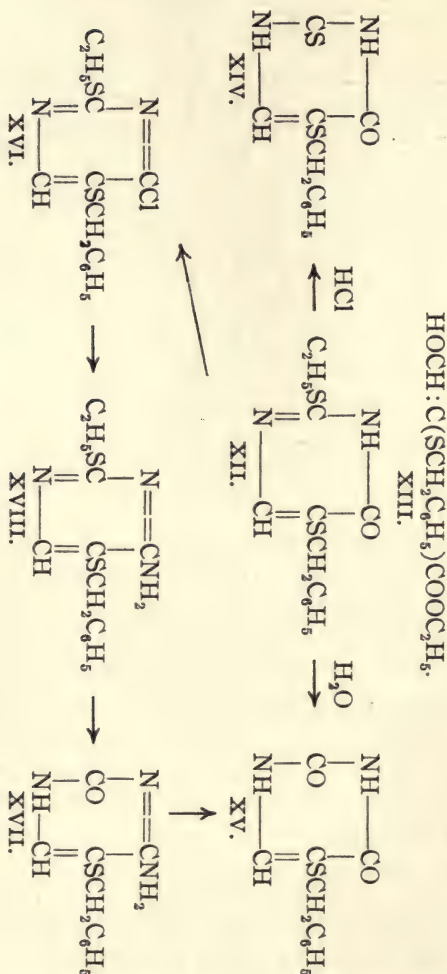
¹ Gabriel: Ber. d. chem. Ges., **12**, 1641.

² Wheeler and Johnson: THIS JOURNAL, **26**, 198.

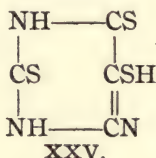
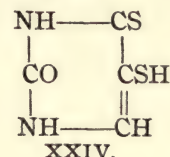
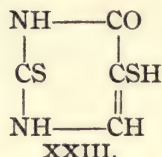
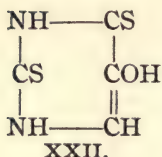
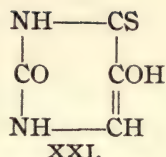
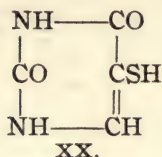
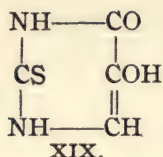


The study of the properties of this pyrimidine was of particular interest because it is the first mercaptopyrimidine to be described which has the mercapto group linked to the 5-position of the pyrimidine ring. Our previous work in this laboratory has been confined to the study of 2- and 4- or 6-mercapto derivatives. The 5-mercapto group in 2-ethylmercapto-5-benzylmercapto-6-oxypyrimidine (XII) is very firmly bound and is not removed by hydrolysis with acids. When the pyrimidine was digested with concentrated hydrochloric acid, it was converted quantitatively into 5-benzylmercaptouracil (XV). On the other hand, when heated above its melting point in a stream of dry hydrochloric acid gas, it was converted smoothly into 2-thio-5-benzylmercapto-6-oxypyrimidine (XIV).

2-Ethylmercapto-5-benzylmercapto-6-oxypyrimidine reacted in a smooth manner with phosphorus oxychloride, giving 2-ethylmercapto-5-benzylmercapto-6-chlorpyrimidine (XVI). When this chlorpyrimidine was heated with ammonia, a quantitative yield of 2-ethylmercapto-5-benzylmercapto-6-aminopyrimidine (XVIII) was obtained. This compound was then converted quantitatively into 5-benzylmercaptocytosine (XVII) by hydrolysis with hydrochloric acid. These different transformations are represented by the following formulas:



There are 7 possible thiopyrimidines that can be derived from 5-hydroxyuracil by replacement of the oxygen atoms with sulphur, *viz.*, the three monothio derivatives, 2-thio-5-hydroxy-6-oxy-, 2,6-dioxy-5-mercapto-, and 2-oxy-5-hydroxy-6-oxypyrimidines (XIX, XX, XXI), the three dithio derivatives, 2,6-dithio-5-hydroxy-, 2-thio-5-mercapto-6-oxy-, and 2-oxy-5-mercapto-6-thiopyrimidines (XXII, XXIII, XXIV), and finally 2,6-dithio-5-mercaptopyrimidine (XXV).



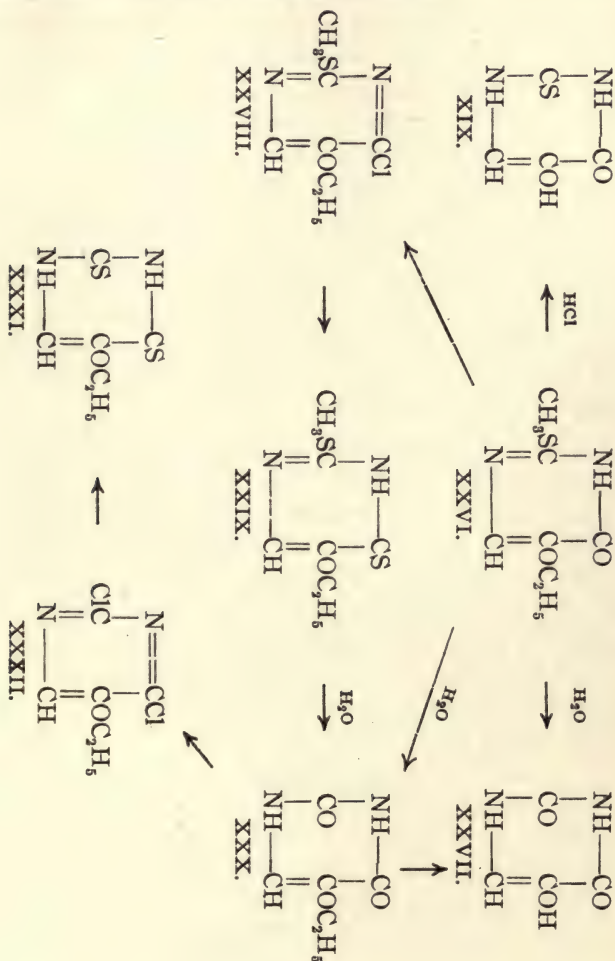
5-Benzylmercaptouracil (XV) and 2-thio-5-benzylmercapto-6-oxypyrimidine (XIV) are the benzyl ethers of 2,6-dioxy-5-mercaptopyrimidine (XX) and 2-thio-5-mercapto-6-oxypyrimidine (XXIII), respectively, and also the first thio ethers of this series of thiopyrimidines to be described.

We have prepared the first member of the series, 2-thio-5-hydroxy-6-oxypyrimidine (XIX), by heating 2-methylmercapto-5-ethoxy-6-oxypyrimidine¹ (XXVI) in a stream of dry hydrochloric acid gas.² An attempt was also made to synthesize 2-oxy-5-hydroxy-6-thiopyrimidine (XXI) from 2-methylmercapto-5-ethoxy-6-oxypyrimidine. The latter compound reacted smoothly with phosphorus oxychloride, giving 2-methylmercapto-5-ethoxy-6-chlorpyrimidine (XXVIII), which was then converted into 2-methylmercapto-5-ethoxy-6-thiopyrimidine (XXIX) by the action of potassium hydrosulphide. All attempts to hydrolyze this pyrimidine to 2-oxy-5-ethoxy-6-thiopyrimidine and 2-oxy-5-hydroxy-6-thiopyrimidine (XXI) were unsuccessful. The 6-sulphur atom is not firmly bound and the pyrimidine underwent hydrolysis with formation of methyl mercaptan and hydrogen sulphide

¹ Johnson and McCollum: J. Biol. Chem., **1**, 447.

² Wheeler and Liddle: J. Am. Chem. Soc., **30**, 1157.

and was converted into 5-ethoxyuracil (XXX). 2,6-Dichloro-5-ethoxypyrimidine (XXXII) was prepared by the action of phosphorus oxychloride on 5-ethoxyuracil (XXX). When this dichloropyrimidine was warmed with potassium hydrosulphide it was converted quantitatively into the ethyl ether of 2,6-dithio-5-hydroxypyrimidine (XXIII) or 2,6-dithio-5-ethoxypyrimidine (XXXI). These various transformations are represented by the following formulas:



EXPERIMENTAL PART.

Ethyl Benzylthioglycollate, $C_6H_5CH_2SCH_2COOC_2H_5$.—This ester has been described by Gabriel,¹ who prepared it by esterification of benzylthioglycollic acid with ethyl alcohol. We prepared it by the action of sodium benzylmercaptide on ethyl chloracetate. The benzyl mercaptan was dissolved in alcohol containing a molecular proportion of sodium ethylate and the required amount of ethyl chloracetate added. The solution was then heated on the steam bath until it failed to give an alkaline reaction, cooled, and the undissolved sodium chloride filtered off. The excess of alcohol was then removed by heating the mixture to 120° and the crude ester washed with water, dissolved in the ether, and dried over calcium chloride. It was purified by one distillation under diminished pressure and the fraction boiling within 10 degrees at a constant pressure saved for our experiments. The boiling points of four different preparations were 190° – 200° at 30–33 mm., 185° – 200° at 33 mm., 198° – 210° at 50 mm., and 179° – 189° at 23 mm. Thirty-two, 35 and 72 grams of the distilled thioglycollic ester were obtained from 34, 38 and 75 grams, respectively, of benzyl mercaptan.

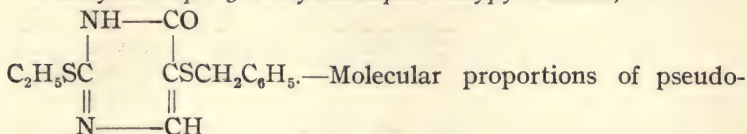
Ethyl α -Benzylmercapto- β -hydroxyacrylate, $HOCH:C(SCH_2C_6H_5)COOC_2H_5$.—The sodium salt of this ester was prepared by adding a mixture of 32 grams of ethyl benzylthioglycollate and 20 grams of ethyl formate, in small portions, to dry ether in which was suspended 4 grams of finely divided sodium. The salt began to deposit at once as a yellow powder, and within 24 hours the sodium had completely disappeared and the condensation was complete. The yield of crude salt was 45 grams. When the salt was dissolved in water and the solution acidified with hydrochloric acid the acrylic ester separated as an oil which solidified when cooled at 0° . After drying in a vacuum over potassium hydroxide and sulphuric acid it melted at 57° – 58° to a clear oil. The ester was very soluble in the common organic solvents and reacted with ferric chloride, giving a bright red color. An attempt to dis-

¹ Ber. d. chem. Ges., 12, 1641.

til it under diminished pressure was unsuccessful. Sulphur determination (Carius): 0.2527 gram substance gave 0.2654 gram of BaSO₄.

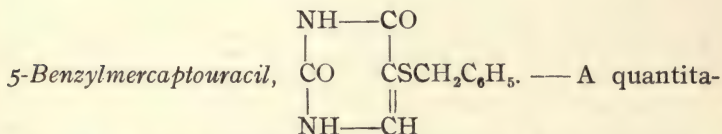
	Calculated for C ₁₂ H ₁₄ O ₂ S.	Found.
S	13.44	14.4

2-Ethylmercapto-5-benzylmercapto-6-oxy pyrimidine,



ethylthiourea hydrobromide (28 grams) and potassium hydroxide (8.5 grams) were dissolved in water and the solutions added successively to a cold, aqueous solution of 45 grams of the sodium salt of ethyl α -benzylmercapto- β -hydroxyacrylate. The mixture was then allowed to stand at ordinary temperature for about 12–14 hours and heated one hour on the steam bath to complete the reaction. The alkaline solution was then cooled, filtered, and acidified with hydrochloric acid. A heavy oil separated and finally crystallized in prisms, melting at 150°–153° to a clear oil. The weight of this crude pyrimidine was 10 grams, and 2 grams more were obtained by extracting the acid solution with ether. The pyrimidine is insoluble in water and difficultly soluble in ether. It crystallizes from 95 per cent. alcohol in four- and six-sided, tabular crystals, which melt at 155°–156° to a clear oil without effervescence. The pyrimidine dissolves in dilute sodium hydroxide solution and is reprecipitated unaltered by addition of acids. Analysis (Kjeldahl):

	Calculated for C ₁₃ H ₁₄ ON ₂ S ₂ .	Found.
N	10.07	10.10



tive yield of this pyrimidine was obtained by digesting 2-

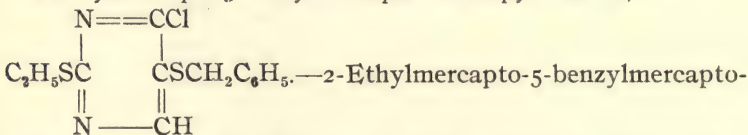
ethylmercapto-5-benzylmercapto-6-oxypyrimidine (3 grams) with strong hydrochloric acid for 4 hours. It is difficultly soluble in hot water and cold alcohol. It crystallizes from boiling 95 per cent. alcohol in rhombic plates or tables, which melt at 290° to a clear oil with decomposition. They gave a strong test for uracil when treated with bromine water and barium hydroxide. Analysis (Kjeldahl):

	Calculated for $C_{11}H_{10}O_2N_2S$.	Found.
N	11.96	11.74

Five-tenths gram of this pyrimidine was heated with 10 cc. of concentrated hydrochloric acid at 130° – 140° for 2 hours. It was recovered unaltered and melting sharply at 290° . The pyrimidine was then heated again at 160° – 170° for 3 hours, when it had been partly decomposed. However, even after this energetic treatment, a small amount of the pyrimidine was recovered unaltered and melting at 290° .

This pyrimidine also dissolves in boiling aniline without change and separates on cooling in plates melting at 290° .

2-Ethylmercapto-5-benzylmercapto-6-chlorpyrimidine,

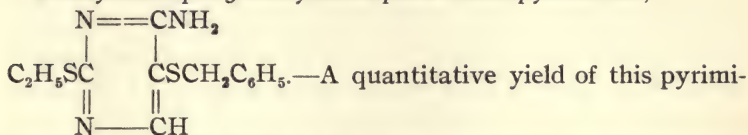


6-oxypyrimidine reacts smoothly with phosphorus oxychloride, giving this chlorpyrimidine. Ten grams of the mercapto-pyrimidine and 40 cc. of phosphorus oxychloride were heated at 120° for 45 minutes, when the evolution of hydrochloric acid had practically ceased. The excess of phosphorus halide was then expelled by heating at 100° under diminished pressure, when a viscous oil was obtained. This was poured into water, warmed gently to decompose any double compound of phosphorus oxychloride, and then extracted with ether. After drying over calcium chloride and evaporating the ether, we obtained the chlorpyrimidine in the form of a dark oil. This solidified on cooling and melted at 40° – 45° . The pyrimidine crystallizes from ligroin in prisms melting at 47° – 48° .

to a clear oil. It is extremely soluble in benzene and alcohol, but insoluble in water. Analysis (Kjeldahl):

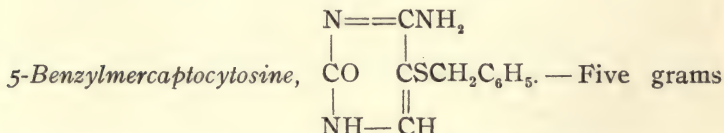
	Calculated for $C_{12}H_{12}N_2ClS_2$.	Found.
N	9.44	9.8

2-Ethylmercapto-5-benzylmercapto-6-aminopyrimidine,



dine was obtained when 5 grams of the above chlorpyrimidine were heated with an excess of an alcoholic solution of ammonia, at 120° – 140° , for 2 hours. After evaporating the excess of alcohol at 100° , the pyrimidine was then separated from ammonium chloride by dissolving it in ether. It is very soluble in ether, ligroin, alcohol and benzene, but insoluble in water. It crystallizes from ligroin in sheaves of needles melting at 68° – 69° to a clear oil. Analysis (Kjeldahl):

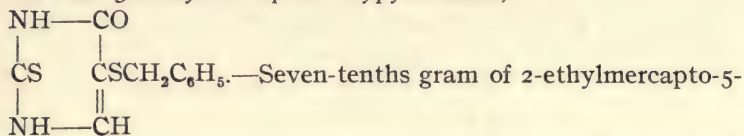
	Calculated for $C_{13}H_{15}N_3S_2$.	Found.
N	15.16	14.88



of 2-ethylmercapto-5-benzylmercapto-6-aminopyrimidine were dissolved in 50 cc. of strong hydrochloric acid and the solution boiled for 1.5 hours, when the evolution of ethyl mercaptan had practically ceased. The solution was then evaporated to dryness, the hydrochloride dissolved in water, and the pyrimidine base precipitated by addition of ammonia. It is soluble in hot alcohol and insoluble in water and ether. It crystallizes from 95 per cent. alcohol in plates melting at 240° – 241° . Analysis (Kjeldahl):

	Calculated for $C_{11}H_{11}ON_3S$.	Found.
N	18.01	18.00

2-Thio-5-benzylmercapto-6-oxy-pyrimidine,

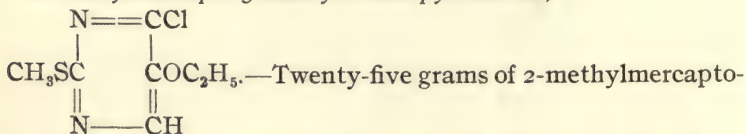


benzylmercapto-6-oxy-pyrimidine was heated in a current of dry hydrochloric acid gas, at 160° – 170° , until the evolution of ethyl chloride ceased. We obtained a brown substance, which was washed with ether to remove traces of oil and then crystallized from 95 per cent. alcohol. The pyrimidine separated, on cooling, in blocks melting at 195° – 196° to an oil without effervescence. It gave a strong test for sulphur. Analysis (Kjeldahl):

	Calculated for $\text{C}_{11}\text{H}_{10}\text{ON}_2\text{S}_2$.	Calculated for $\text{C}_4\text{H}_4\text{ON}_2\text{S}_2$.	Found.
N	11.20	17.50	11.57

Attempts to prepare this pyrimidine by condensation of the sodium salt of ethyl α -benzylmercapto- β -hydroxyacrylate with thiourea in aqueous solution, and in alcohol in presence of sodium ethylate, were unsuccessful. For example: one gram of sodium and 3 grams of thiourea were dissolved in alcohol, ten grams of the sodium salt suspended in the solution, and the mixture then digested on the steam bath for 6 hours. There was no indication of any reaction and 8.0 grams of the unaltered sodium salt separated on cooling. The alcohol filtrate was then evaporated to dryness and the residue left behind dissolved in a little cold water and the solution carefully acidified with hydrochloric acid. The solution became turbid, but on standing no pyrimidine separated, showing that no condensation had taken place.

2-Methylmercapto-5-ethoxy-6-chlorpyrimidine,



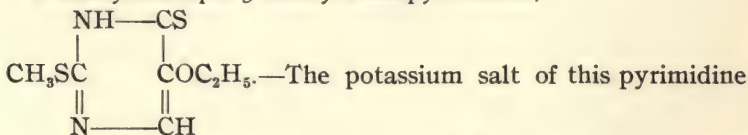
5-ethoxy-6-oxy-pyrimidine¹ were suspended in 40 cc. of phos-

¹ Johnson and McCollum: *Loc. cit.*

phorus oxychloride. There was an immediate reaction and the pyrimidine dissolved completely. The solution was heated in an oil bath at 120° – 130° for a few hours to complete the reaction, and the excess of phosphorus oxychloride removed by heating at 100° under diminished pressure. An oil was obtained which immediately solidified when poured into cold water. This was a double compound of the pyrimidine and phosphorus oxychloride, and in order to decompose it and destroy the phosphorus halide, it was necessary to triturate it with hot water. The pyrimidine was then dissolved in ether, washed with dilute sodium hydroxide solution and dried over calcium chloride. When the ether was removed we obtained the pyrimidine as a crystalline solid melting at 70° . The yield was 21 grams, or 95 per cent. of the calculated. The pyrimidine is insoluble in water and very soluble in benzene and ether. It crystallizes from 95 per cent. alcohol in slender prisms melting at 75° to an oil. Analysis (Kjeldahl):

	Calculated for $C_7H_5ON_2ClS$.	Found.
N	13.69	13.63

2-Methylmercapto-5-ethoxy-6-thiopyrimidine,

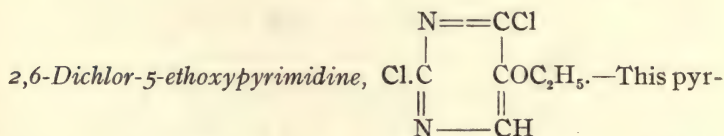


was obtained when 5 grams of 2-methylmercapto-5-ethoxy-6-chlorpyrimidine were dissolved in an alcoholic solution of potassium hydrosulphide and the mixture digested on the steam bath for several hours. The excess of alcohol was then removed by evaporation at 100° and the potassium salt of the pyrimidine and potassium chloride dissolved in water. When this solution was acidified with acetic acid, the 6-thiopyrimidine separated in yellow crystals. It is difficultly soluble in hot water but crystallizes from alcohol in light yellow prisms melting at 190° to a clear oil. The yield was 3.5 grams. Analysis (Kjeldahl):

	Calculated for $C_7H_{10}ON_2S_2$	Found.
N	13.86	13.78

An attempt to prepare 2-oxy-5-ethoxy-6-thiopyrimidine from this compound, by hydrolysis with hydrochloric acid, was unsuccessful. About 7 grams of the mercaptopyrimidine were digested with a large excess of concentrated hydrochloric acid on the steam bath for several hours. Methyl mercaptan and hydrogen sulphide were evolved and the pyrimidine finally dissolved. The acid solution was then evaporated to dryness and the crystalline substance obtained purified by repeated crystallizations from hot water. It separated in irregular prisms which melted at about 275° to a dark oil. This melting point varies according to the rate of heating. The compound gave no test for sulphur, and a nitrogen determination (Kjeldahl) agreed with the calculated value for 5-ethoxyuracil.¹ The small amount of material which accompanied this 5-ethoxypyrimidine and rendered the purification difficult contained sulphur, but we did not succeed in isolating a sufficient quantity of the substance in pure state for analysis. Its melting point, 190° – 230° , indicated a mixture.

	Calculated for $C_6H_8O_2N_2$	Found.
N	17.94	17.80



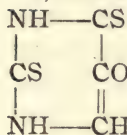
imidine was prepared by the action of phosphorus oxychloride on 5-ethoxyuracil.¹ Twelve grams of the ethoxyuracil and 70 cc. of phosphorus oxychloride were digested at 120° – 130° for nearly 3 hours before the evolution of hydrochloric acid ceased. The dark liquid was then filtered from a small amount of insoluble, amorphous substance and the excess of phosphorus halide removed, in the usual manner, by heating at 100° under diminished pressure. We obtained a thick syrup

¹ Johnson and McCollum: *Loc. cit.*

which solidified when poured into cold water. In order to destroy all phosphorus halide, this substance was then melted under water by heating the liquid to 60° – 70° , and after thorough mixing the pyrimidine was dissolved in ether. The ether solution was then dried over calcium chloride and the excess of ether removed by spontaneous evaporation, when the pyrimidine separated in well-developed prisms. It is soluble in cold alcohol, benzene and petroleum ether and crystallizes from the latter in clusters of radiating prisms and needles which melt at 41° – 42° to a clear oil. It crystallizes from water in prisms melting at the same temperature. The yield was about 75 per cent. of the calculated. Analysis (Kjeldahl):

	Calculated for $C_6H_6ON_2Cl_2$.	Found.
N	14.50	14.35

2,6-Dithio-5-ethoxypyrimidine (5-Ethoxydithiouracil),



—This compound was prepared by the action of potassium hydrosulphide on 2,6-dichlor-5-ethoxypyrimidine in alcoholic solution. It is soluble in hot alcohol and crystallizes, on cooling, in needles which slowly decompose when heated above 255° , and effervesce violently at about 267° – 268° . The pyrimidine is insoluble in water. Analysis (Kjeldahl):

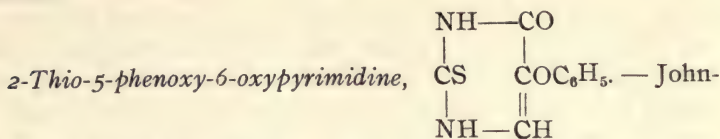
	Calculated for $C_6H_6ON_2S_2$.	Found.
N	14.7	14.9

Sodium Salt of Ethyl α -Phenoxy- β -hydroxyacrylate,

$\text{NaOCH:C(OC}_6\text{H}_5\text{)COOC}_2\text{H}_5$.—Johnson and Heyl¹ prepared this salt by condensation of ethyl formate with ethyl phenoxyacetate in presence of sodium ethylate. The use of sodium ethylate is unnecessary and a practically quantitative yield of the salt can be obtained if the esters are condensed in ether in the presence of metallic sodium. Thirty-one grams of

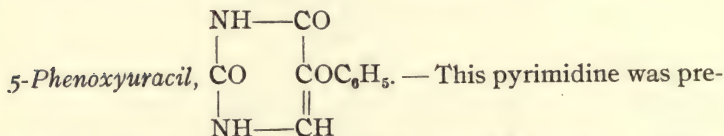
¹ THIS JOURNAL, 37, 636.

crude, dry salt were obtained from 25 grams of ethyl phenoxyacetate.



son and Heyl¹ have shown that the above sodium salt condenses with pseudoethylthiourea, in aqueous solution, giving 2-ethylmercapto-5-phenoxy-6-oxypyrimidine. Fifteen grams of thiourea and 4.5 grams of sodium were dissolved in alcohol and 31 grams of the sodium salt dissolved in the solution by warming on the steam bath. After digesting for 10 hours, the excess of alcohol was removed by evaporation at 100° and the residue remaining dissolved in cold water, filtered, and the solution acidified with acetic acid. Sixteen grams of the crude pyrimidine separated as a colorless, granular powder. It is insoluble in hot water, moderately soluble in alcohol, insoluble in benzene and soluble in acetic acid. It crystallizes from acetic acid in clusters of prisms showing a twinning habit, and melts at 253°–254° to a brown oil. Nitrogen (Kjeldahl) and sulphur (Carius) determinations gave the following results:

	Calculated for $\text{C}_{10}\text{H}_9\text{O}_2\text{N}_2\text{S}$.	I.	Found.	II.
N	12.73	12.82		...
S	14.56	14.30		14.72



pared by heating 2-thio-5-phenoxy-6-oxypyrimidine (2 grams) with concentrated hydrochloric acid (35 cc.) at 140°–160°, and also by digestion with hydrobromic acid for several hours. It is practically insoluble in cold water and alcohol and difficultly soluble in hot water. It crystallizes from boiling acetic acid

¹ *Loc. cit.*

in distorted needles melting at 290° with effervescence. Analysis (Kjeldahl):

	Calculated for $C_{10}H_8O_3N_2$.	Found.
N	13.72	13.62

NEW HAVEN, CONN.,
June, 1909.

[Contributions from the Sheffield Laboratory of Yale University.]

CLXXI.—RESEARCHES ON PYRIMIDINES:

DIMETHYL DERIVATIVES OF 2-AMINOPYRIMIDINE.
PREPARATION OF 2-METHYLAMINO-5-METHYL-
PYRIMIDINE.

[FORTY-SIXTH PAPER.]

BY TREAT B. JOHNSON AND KENNETH G. MACKENZIE.¹

This paper is a preliminary contribution to the study of aminomethylpyrimidines having the empirical formula $C_6H_9N_3$. Our interest in aminopyrimidines of this composition was incited by a paper entitled "Ueber die chemische Zusammensetzung der japanischen Soja-Souce oder Schōyu,"² in which the authors have described two decomposition products of *Schōyu* to which they have assigned the empirical formulas $C_6H_9N_3$ and $C_4H_{12}N_2$. They state that the substance, $C_6H_9N_3$, is probably an isomer of aminodimethylpyrimidine, but is not identical with any one of three pyrimidines of this constitution which have been described in the literature,³ viz., 2,6-dimethyl-4-aminopyrimidine,⁴ 2-amino-4,5-dimethylpyrimidine,⁵ and 2-amino-4,6-dimethylpyrimidine.⁶

¹ A part of this paper was presented as a thesis by Mr. Kenneth Gerard Mackenzie to the Faculty of the Graduate School of Yale University for the Degree of Master of Science (June, 1909).

² Suzuki, Aso, and Mitarai: Bull. Coll. Agriculture (Tokio Univ.), **7**, 477 (1907).

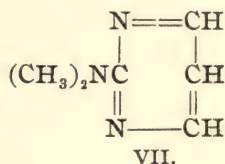
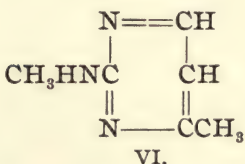
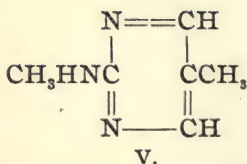
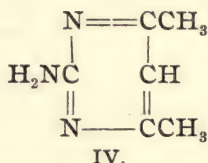
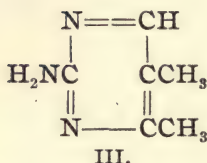
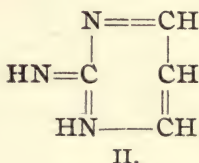
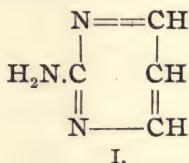
³ The Japanese investigators failed to recognize that a fourth isomer, 4,5-dimethyl-6-aminopyrimidine, has been prepared by Schlenker (Ber. d. chem. Ges., **34**, 2823). No salts of this pyrimidine have been described.—T. B. J.

⁴ Schwarze: J. prakt. Chem., **42**, 1 (1889). Schmidt: Ber. d. chem. Ges., **35** 1577 (1902).

⁵ Schlenker: Ber. d. chem. Ges., **34**, 2819 (1901).

⁶ Angerstein: Ber. d. chem. Ges., **34**, 3962.

If we disregard the tautomeric form of 2-aminopyrimidine¹ (II), there are only five possible dimethyl derivatives of this pyrimidine (I), viz., the two isomers described in the literature, 4,5-dimethyl²- and 4,6-dimethyl-2-aminopyrimidine³ (III and IV), 2-methylamino-5-methylpyrimidine (V), 2-methylamino-4-methylpyrimidine (VI), and 2-dimethylaminopyrimidine (VII).



We shall describe, in this paper, the preparation and properties of 2-methylamino-5-methylpyrimidine (V), and also some derivatives of the isomeric 2-methylamino-4-methylpyrimidine (VI). A description of a new method of preparing thymine has also been appended to this paper.

It has been shown in several papers from this laboratory⁴ that aryl substituted aminopyrimidines can be obtained, in practically quantitative yields, by heating 2-mercaptopyrimidines with aromatic bases. The action of aliphatic amines on mercaptopyrimidines has not been investigated. Since

¹ Büttner: Ber. d. chem. Ges., **36**, 2229.

² Schlenker: *Loc. cit.*

³ Angerstein: *Loc. cit.*

⁴ Wheeler and Bristol: THIS JOURNAL, **33**, 438, 448. Johnson and Johns: *Ibid.*, **34**, 175. Johnson and Heyl: *Ibid.*, **38**, 238. Johnson and Storey: *Ibid.*, **40**, 131.

it was necessary for us to devise a practical method of preparing alphyaminopyrimidines easily and in sufficient quantities for our work, we therefore investigated the action of methylamine on some 2-mercaptopyrimidines.

We now find that 2-methylmercapto-5-methyl-6-oxypyrimidine¹ (VIII), and 2-methylmercapto-4-methyl-6-oxypyrimidine² (IX), react with methylamine at 140°–150°, giving quantitative yields of 2-methylamino-5-methyl-6-oxypyrimidine (X) and 2-methylamino-4-methyl-6-oxypyrimidine (XI), respectively. The latter pyrimidine was identical with the 2-methylaminopyrimidine obtained by Jäger³ by alkylation of 2-amino-4-methyl-6-oxypyrimidine⁴ with methyl iodide. The same pyrimidine has also recently been prepared by Majima⁵ by condensing methylguanidine with ethyl acetate. The yield by this method, however, corresponds to only about 50 per cent. of the theoretical, because part of the methylguanidine condenses, giving the isomeric 2-amino-3,4-dimethyl-6-oxypyrimidine.

These two 2-methylaminopyrimidines, (X) and (XI), reacted smoothly with phosphorus oxychloride, giving practically quantitative yields of 2-methylamino-5-methyl-6-chlorpyrimidine (XII) and 2-methylamino-4-methyl-6-chlorpyrimidine (XIII), respectively. Both of these pyrimidines underwent hydrolysis to the original 6-oxypyrimidines (X) and (XI), when an attempt was made to reduce them with hydriodic acid. On the other hand, they were converted into 2-methylamino-5-methylpyrimidine (V) and 2-methylamino-4-methylpyrimidine (VI), respectively, by reduction with zinc dust. We have not isolated the free 2-methylamino-4-methylpyrimidine,⁶ but have procured evidence of its formation, since we have obtained a picrate of the base and a characteristic zinc chloride double compound of definite

¹ Wheeler and Merriam: *THIS JOURNAL*, **29**, 487.

² List: *Ann. Chem. (Liebig)*, **236**, 12.

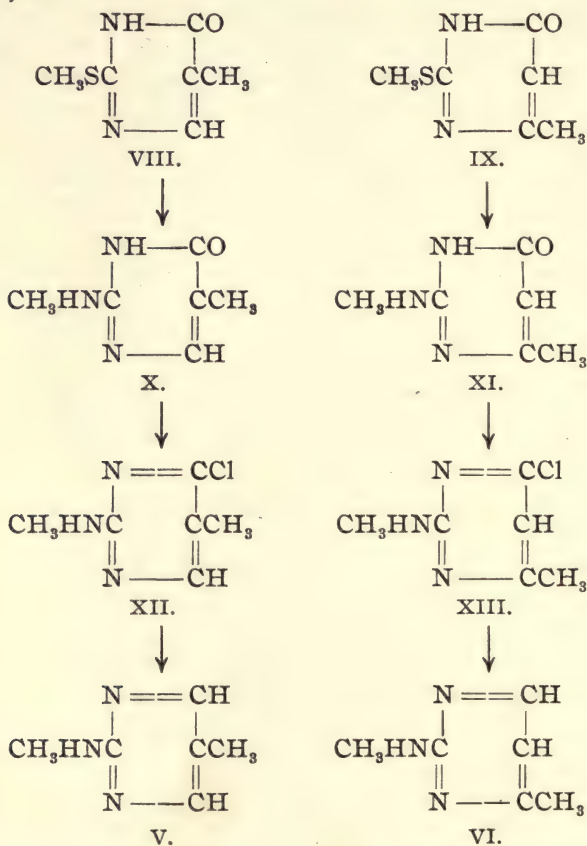
³ *Ann. Chem. (Liebig)*, **262**, 365.

⁴ Jäger: *Loc. cit.* Köhler: *Ber. d. chem. Ges.*, **19**, 220.

⁵ *Ber. d. chem. Ges.*, **41**, 176.

⁶ We were obliged to discontinue experiments on the reduction of 2-methylamino-4-methyl-6-chlorpyrimidine, because of the unexpected departure of one of us from the laboratory and on account of pressure of other work.—T. B. J.

constitution. The experimental evidence indicates that this methylaminopyrimidine is not identical with the base found in *Schöyu*.



2-Methylamino-5-methylpyrimidine (V) is not identical with the base $\text{C}_6\text{H}_9\text{N}_3$ which Suzuki and his coworkers isolated from *Schöyu*. They state that their base reacted with diazobenzenesulphonic acid, in the presence of alkali, giving an intense red color. Our pyrimidine and the diazo reagent gave at first no color, but on long standing a brilliant red color finally developed. A characteristic feature of their base was its tendency to form *acid* salts, *viz.*, the picrate

$C_6H_9N_3(C_6H_3O_7N_3)_2$, decomposing at 230° , and the hydrochloride $C_6H_9N_3 \cdot 2HCl$, melting at 232° – 233° . Our pyrimidines, on the other hand, are characterized by their tendency to form basic salts. The isomeric picrates, $(C_6H_9N_3)_2 \cdot C_6H_3O_7N_3$, of 2-methylamino-5-methylpyrimidine and 2-methylamino-4-methylpyrimidine both decomposed when heated above 150° . 2-Methylamino-5-methylpyrimidine formed a hydrous hydrochloride, $(C_6H_9N_3)_2HCl \cdot H_2O$, melting at 162° – 163° . It is an interesting fact that 2-amino-5,6-dimethylpyrimidine¹ is the only dimethyl derivative of 2-aminopyrimidine, so far examined, that forms acid salts, *viz.*, the picrate and hydrochloride.

A New Method of Preparing Thymine.

In a previous paper from this laboratory one of the writers² showed that pseudomethylthiourea condenses smoothly, in aqueous solution, with the sodium salt of diethyl oxalpropionate, giving 2-methylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine. When this acid, in small quantities, is heated above its melting point it undergoes a quantitative decomposition, with evolution of carbon dioxide, giving 2-methylmercapto-5-methyl-6-oxypyrimidine.³ A quantitative yield of thymine is then obtained by hydrolysis of this mercaptopyrimidine. The writer did not, at that time, lay stress on this method of synthesizing thymine because of the progress of other work in this laboratory on different methods of preparing this pyrimidine.

We have now investigated this method of preparation and find that the sodium salt of diethyl oxalpropionate condenses as smoothly, in aqueous solution, with pseudoethylthiourea as with pseudomethylthiourea, giving the corresponding 2-ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine (XIV). This pyrimidine melts lower than the corresponding 2-methylmercapto compound⁴ and undergoes decomposition at its melting point, giving 2-ethylmercapto-5-methyl-6-oxypyrimi-

¹ *Loc. cit.*

² Johnson: *J. Biol. Chem.*, **3**, 299 (1907).

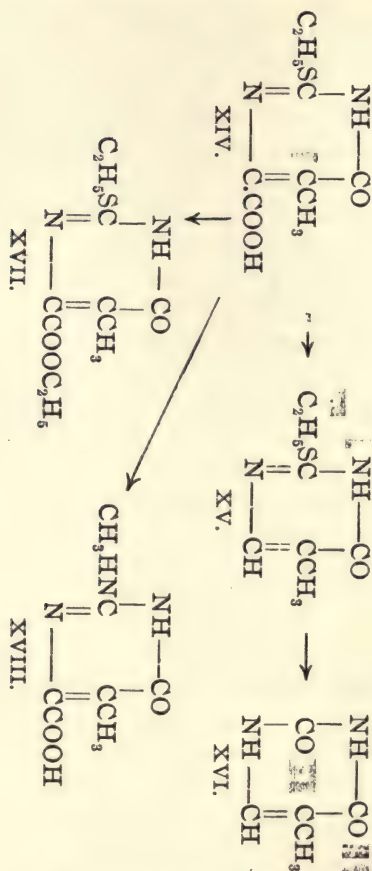
³ Wheeler and Merriam: *Loc. cit.*

⁴ Johnson: *Loc. cit.*

dine¹ (XV), which can be converted into thymine (XVI) by hydrolysis with hydrochloric acid. The success of this method of preparation was evidently dependent upon the fact whether large amounts of the mercapto acid (XIV) could be changed smoothly and quantitatively into 2-ethylmercapto-5-methyl-6-oxypyrimidine.² Working with small quantities, less than 15-16 grams of the acid, the decomposition into 2-ethylmercapto-5-methyl-6-oxypyrimidine was practically quantitative and the final yield of thymine corresponded to nearly 85-90 per cent. of the theoretical. On the other hand, when large amounts of 2-ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine are decomposed under the same conditions the method is not practicable because it is then necessary to heat a long time, at a high temperature, in order to complete the reaction. Under such conditions secondary reactions set in with formation of products which contaminate the 2-ethylmercapto-5-methyl-6-oxypyrimidine and render its purification difficult. It is probable that these mercaptopyrimidines, when heated at high temperatures and in presence of impurities, slowly undergo dissociation into ethylene hydrocarbons and 2-thiopyrimidines. The ethyl ester of 2-ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine (XVII) was obtained in one experiment as the chief product of the condensation. It was also formed quantitatively by the action of ethyl iodide on the silver salt of the mercapto acid (XIV). When the mercapto acid (XIV) was heated with methylamine, a quantitative yield of 2-methylamino-4-carboxyl-5-methyl-6-oxypyrimidine (XVIII) was obtained. These various transformations are represented by the following formulas:

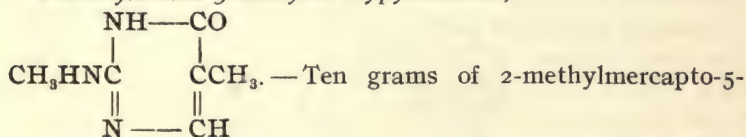
¹ Wheeler and Johnson: *THIS JOURNAL*, **31**, 595.

² *Loc. cit.*



EXPERIMENTAL PART.

2-Methylamino-5-methyl-6-oxypyrimidine,



methyl-6-oxypyrimidine¹ were heated with 18 grams of 33 per cent. methylamine solution (6 grams CH_3NH_2) at 140° – 150° for two hours. The clear solution was then transferred to a dis-

¹ *Loc. cit.*

tillation flask and the excess of methylamine expelled by passing a current of air through the boiling solution. On cooling, 8 grams of the aminopyrimidine separated, corresponding to 91 per cent. of the theoretical yield. In two other experiments, when 6 grams of the 2-methylmercaptopyrimidine were heated with 7.2 grams of 33 per cent. methylamine solution, under the same conditions, we obtained 5.0 and 5.3 grams of the crude pyrimidine.

This 2-methylaminopyrimidine is difficultly soluble in cold, but very soluble in hot water; soluble in boiling alcohol and benzene. It crystallizes from water in colorless, hairy crystals, which melt at 213° to a clear oil. The pyrimidine is characterized by its tendency to form supersaturated, aqueous solutions. It reacts with diazobenzenesulphonic acid in presence of sodium hydroxide, giving a strong, claret-red color. It contained one molecule of water of crystallization, which was determined by heating at 100° – 110° for one hour.

0.5821 gram substance lost 0.0584 gram H_2O .

	Calculated for $C_6H_9ON_3 \cdot H_2O$.	Found.
H_2O	11.4	10.03

Nitrogen determination in anhydrous substance (Kjeldahl):

	Calculated for $C_6H_9ON_3$.	Found.
N	30.22	30.23

Sulphate, $C_6H_9ON_3 \cdot H_2SO_4$.—Five-tenths gram of the pyrimidine base and 0.7 gram of sulphuric acid were dissolved in water and the solution allowed to concentrate in the air. The salt finally crystallized in large, transparent, tabular crystals, which melted at 202° to a brown oil. The salt is insoluble in alcohol but very soluble in water. It was dried at 100° for analysis (Kjeldahl):

	Calculated for $C_6H_9ON_3 \cdot H_2SO_4$.	I.	Found.	II.
N	17.72	17.51		17.83

Picrate, $(C_6H_9ON_3)_2 \cdot C_6H_3O_7N_3 \cdot H_2O$.—This salt was prepared by adding a solution of picric acid to an aqueous solution of the base. The picrate deposited in distorted prisms

which melted with decomposition at 240° . Analysis (Kjeldahl):

Calculated for $C_6H_9ON_3 \cdot C_6H_3O_7N_3$ = 22.82 per cent N.
 Calculated for $C_6H_9ON_3 \cdot (C_6H_3O_7N_3)_2$ = 21.10 per cent N.
 Calculated for $(C_6H_9ON_3)_2 \cdot C_6H_3O_7N_3 \cdot H_2O$ = 24.00 per cent N.

	I.	II.	III.	IV.
Nitrogen found:	23.89	24.12	24.20	24.25

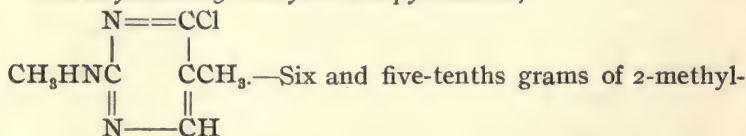
Platinum Chloride Salt, $(C_6H_9ON_3 \cdot HCl)_2 \cdot PtCl_4$, was prepared by addition of hydrochloroplatinic acid to an aqueous solution of the pyrimidine base. It did not contain water of crystallization. Platinum determinations:

I. 0.0889 gram of salt gave 0.0248 gram of Pt.

II. 0.0989 gram of salt gave 0.0277 gram of Pt.

	Calculated for $(C_6H_9ON_3 \cdot HCl)_2 \cdot PtCl_4$.	I.	Found. II.
Pt	28.3	27.90	28.06

2-Methylamino-5-methyl-6-chlorpyrimidine,

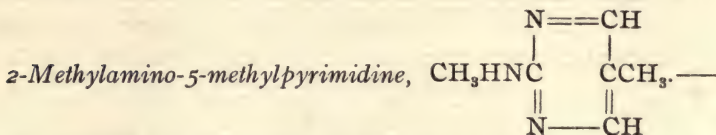


amino-5-methyl-6-oxypyrimidine were dissolved, by warming, in 30 cc. of phosphorus oxychloride and the solution boiled for 30 minutes. The excess of phosphorus oxychloride was then removed by heating at 100° under diminished pressure, when a viscous liquid was obtained. This was dissolved in cold water and the solution made alkaline with sodium hydroxide, when the chlorpyrimidine separated. After drying in a vacuum over concentrated sulphuric acid it weighed 6.9 grams, corresponding to 95 per cent. of the theoretical. In a second experiment, when we used 10.6 grams of the 2-methylmercaptopyrimidine and 53 cc. of phosphorus oxychloride we obtained a yield of 11.5 grams of the chlorpyrimidine.

The pyrimidine is insoluble in water but soluble in alcohol and benzene. It sublimes at 100° and melts at 131° to a

clear oil with no effervescence. It crystallizes from 95 per cent. alcohol in prismatic crystals. Analysis (Kjeldahl):

	Calculated for $C_6H_9N_3Cl$.	Found.
N	26.67	26.83



Five grams of 2-methylamino-5-methyl-6-chlorpyrimidine and 15 grams of zinc dust were suspended in 200 cc. of water and the mixture digested for 8 hours. The excess of zinc was then removed by filtration and the filtrate concentrated on the steam bath. We obtained a thick syrup which was dissolved in 25 cc. of water and an excess of a saturated, aqueous solution of potassium hydroxide added. A light colored precipitate was formed which was filtered by suction, and dried in a desiccator over sulphuric acid.

An attempt to purify this substance by sublimation was unsuccessful. The crude, dry material was finally extracted several times with boiling ether. When the excess of ether was evaporated, about 2 grams of a colorless, crystalline substance which melted at 97° – 100° to a clear oil was obtained. In order to purify it for analysis it was dissolved in dry ligroin and the solution allowed to concentrate by slow evaporation. The pyrimidine separated under these conditions in beautiful, transparent prisms, which melted sharply at 102° to a clear oil. The pyrimidine is extremely soluble in cold water, ether, and benzene. It showed no alkaline reaction when tested with turmeric and was precipitated from an aqueous solution by mercuric chloride. It gave at first no color when tested with diazobenzenesulphonic acid, but on allowing the mixture to stand a strong red color finally developed. The pyrimidine sublimes when heated above 100° . Analysis:

	Calculated for $C_6H_9N_3$.	Found.
N	34.14	34.20

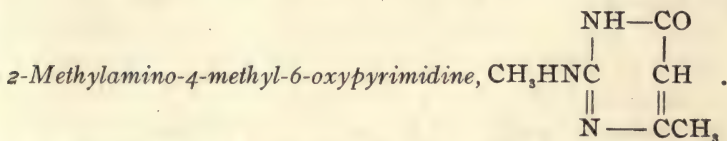
An attempt was made to reduce the 6-chlorpyrimidine with hydriodic acid, but it underwent hydrolysis, giving 2-methylamino-5-methyl-6-oxypyrimidine.

Picrate, $(C_6H_9N_3)_2 \cdot C_6H_3O_7N_3$.—This salt separated immediately when an aqueous solution of picric acid was added to a solution of the pyrimidine base. It had no definite melting point, but began to shrivel at about 100° and decomposed when heated above 150° . Analysis:

	Calculated for $(C_6H_9N_3)_2 \cdot C_6H_3O_7N_3$.	Found.
N	26.53	26.36

Hydrochloride, $(C_6H_9N_3)_2 \cdot HCl \cdot H_2O$.—This salt was prepared by dissolving the base in warm hydrochloric acid and concentrating the solution on the steam bath. It was extremely soluble in water, but crystallized from methyl alcohol in well-developed prismatic crystals. The salt melts at 162° – 163° to a clear oil and does not effervesce below 250° . Analysis:

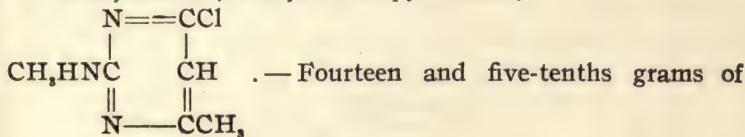
	Calculated for			Found.	
	$C_6H_9N_3 \cdot HCl$.	$C_6H_9N_3 \cdot 2HCl$.	$(C_6H_9N_3)_2 \cdot HCl \cdot H_2O$.	I.	II.
N	26.33	21.64	27.95	27.7	27.88



—We prepared this pyrimidine¹ by heating 2-methylmercapto-4-methyl-6-oxypyrimidine¹ with an excess of methylamine at 140° – 150° . The yield was quantitative and the pyrimidine melted at 201° – 202° after one recrystallization from hot water. Analysis (Kjeldahl):

	Calculated for $C_6H_9ON_3$.	Found.
N	30.22	30.00

2-Methylamino-4-methyl-6-chlorpyrimidine,



¹ *Loc. cit.*

2-methylamino-4-methyl-6-oxypyrimidine and 72 cc. of phosphorus oxychloride were heated in an oil bath at 120° – 130° for 30 minutes, when the evolution of hydrochloric acid gas had practically ceased. We obtained a clear solution which was then heated at 100° under diminished pressure to remove the excess of phosphorus oxychloride. A brown oil remained, which was dissolved in cold water, and the solution made alkaline with sodium hydroxide. The pyrimidine separated in colorless crystals and was dried in a desiccator over sulphuric acid. It is very insoluble in water but easily soluble in alcohol. It separates from an alcohol solution in long needles which melt at 135° to a yellow oil without effervescence. It slowly sublimes when heated above 100° . Analysis (Kjeldahl):

	Calculated for $C_6H_8N_2Cl$.	Found.
N	26.67	26.70

Reduction of 2-Methylamino-4-methyl-6-chlorpyrimidine with Zinc.—This chlorpyrimidine is very slowly reduced by digestion with zinc dust because of the insolubility of the pyrimidine in water. Unaltered chlorpyrimidine was recovered after 12 hours' digestion of 12 grams of the pyrimidine and 50 grams of zinc dust in 1000 cc. of water. One hundred cc. of alcohol were then added and the mixture boiled again for 10 hours, cooled and filtered. By extraction of the zinc residue with alcohol, we recovered 6 grams of unaltered 6-chlorpyrimidine. The aqueous filtrate was concentrated to a volume of 15–20 cc. and allowed to stand at ordinary temperature, when well-developed, red crystals separated. They melted sharply at 170° – 172° to an oil without effervescence and contained zinc and chlorine. The substance was extremely soluble in water and did not lose weight when heated at 100° – 110° . A nitrogen determination (Kjeldahl) agreed with the calculated value for a double compound containing 3 molecules of 2-methylamino-4-methylpyrimidine and one molecule of zinc chloride, $(C_6H_8N_2)_2 \cdot ZnCl_2$:

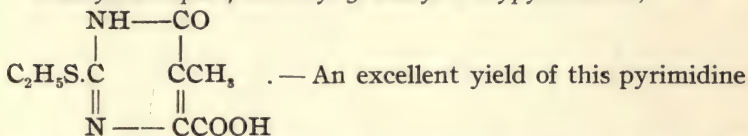
	Calculated for $(C_6H_8N_2)_2 \cdot ZnCl_2$.	Found.
N	22.97	22.80

The filtrate obtained after separation of the zinc chloride compound was concentrated on the steam bath to a viscous liquid and then triturated with about 25 cc. of a strong, aqueous solution of potassium hydroxide. An amorphous substance was precipitated, which was separated by suction filtration, washed with a few drops of cold water, and dried in a desiccator over sulphuric acid. This substance was then extracted in a Soxhlet apparatus with ether for three days. When the ether was evaporated we obtained an oil which dissolved at once in water, alcohol and benzene. In order to establish the presence of 2-methylamino-4-methylpyrimidine, the oil was dissolved in water and a solution of picric acid added to the aqueous solution. A picrate separated at once in the form of irregular prisms which melted at 150°–155° to an oil with no appreciable effervescence. This salt did not give a test for chlorine. Analysis (Kjeldahl):

	Calculated for		Found.
	(C ₆ H ₉ N ₃) ₂ .C ₆ H ₅ O ₇ N ₃ .	C ₆ H ₉ N ₃ .C ₆ H ₅ O ₇ N ₃ .	
N	26.5	23.8	25.98

2-Methylamino-4-methyl-6-chlorpyrimidine was converted into 2-methylamino-4-methyl-6-oxypyrimidine when heated with hydriodic acid.

2-Ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine,



is obtained by condensation of pseudoethylthiourea with the sodium salt of diethyl methyloxalacetate in aqueous solution. In our preliminary experiments this sodium salt was prepared by condensation of diethyloxalate with ethyl propionate in presence of sodium ethylate.¹ We found, however, that the use of dry sodium ethylate is unnecessary and that as good a yield of the salt can be obtained by condensation of the esters in anhydrous ether in presence of metallic sodium. This fact is shown by comparison of the yields of pyrimidine given in the table. Our method of preparing the pyrimidine

¹ Arnold: Ann. Chem. (Liebig), **246**, 329.

was as follows: A mixture of 50 grams of ethyl propionate and 71 grams of diethyl oxalate was added slowly to dry ether, in which was suspended 11.5 grams of metallic sodium. After the esters had been added the mixture was allowed to stand about 2 days to insure a complete reaction. Cold water (about 500–600 cc.) was then cautiously added to dissolve the sodium salt, and the ether layer separated. To this aqueous solution was then added a concentrated, aqueous solution of 52 grams of pseudoethylthiourea hydrobromide and finally two molecular proportions of potassium hydroxide (32 grams). After allowing to stand for 2 days at 40°–50° the solution was concentrated to about one-half its original volume, cooled, and acidified with an excess of strong hydrochloric acid. The pyrimidine usually separated in the form of a light pink or nearly colorless, granular powder melting at 210°–215° with evolution of carbon dioxide. The yield of mercaptopyrimidine is decreased by using, for the condensation, more than two molecular proportions of potassium hydroxide because the pyrimidine is slowly converted into thymine-4-carboxylic acid,¹ with evolution of ethyl mercaptan, when warmed with strong alkaline solutions (Experiment 5 in table).

The proportion of pseudoethylthiourea hydrobromide to be used for a condensation was calculated upon the basis that the yield of sodium salt of diethyl oxalpropionate is only about 50 per cent. of the theoretical (Arnold² says 45 per cent.). Under these conditions, fifty grams of ethyl propionate require for condensation 45 grams of the pseudothiourea salt, which we increased to 52–54 grams or about 0.6 molecular proportion. The yield of pyrimidine was not increased by using more than this proportion (see Experiment 2 in table).

¹ Johnson: J. Biol. Chem., **3**, 299.

² *Loc. cit.*

Table I.

	$\text{CH}_3\text{CH}_2\text{COOC}_2\text{H}_5$ Grams.	$(\text{COOC}_2\text{H}_5)_2$ Grams.	Na used. Grams.	$\text{C}_6\text{H}_5\text{SC}(\text{NH})\text{NH}_2$ HBr . Grams.	KOH used. Grams.	Yield of 2-mercapto-4-carboxyl-5-methyl-6-oxypyrimidine. Grams.
1	50.0	71.0	11.5	52.0	16.0	36.0
2	50.0	71.0	11.5	72.0	22.0	36.5
3	50.0	71.0	11.5	54.0	32.0	34.0
4	50.0	71.0	11.5 in form NaOC_2H_5	54.0	32.0	37.0
5	100.0	144.0	22.5	100.0	108.0 (2.5 mols.)	60.0 and 15.0 of thymine-4-carboxylic acid ¹
6	50.0	71.0	11.5 in form NaOC_2H_5	45.0	30.0	22.0

2-Ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine is soluble in boiling water but separates on cooling in clusters of slender needles and prismatic crystals. It is more soluble in alcohol than in water. It decomposes, after crystallization from water, from 215° – 218° with effervescence, giving 2-ethylmercapto-5-methyl-6-oxypyrimidine² (see below). If the acid is dissolved in dilute sodium hydroxide solution and reprecipitated by addition of hydrochloric acid it separates in colorless crystals melting sharply at 220° . The acid is not precipitated from aqueous solutions of its sodium salt by addition of acetic acid.

Analysis (Kjeldahl):

	Calculated for $\text{C}_8\text{H}_{10}\text{O}_5\text{N}_2\text{S}$.	I.	Found.	II.
N	13.08	13.3		13.2

Stability of the Sodium Salt of Diethyl Oxalpropionate, $\text{C}_2\text{H}_5\text{OOC}.\text{C}(\text{ONa}).\text{C}(\text{CH}_3)\text{COOC}_2\text{H}_5$.—Seventy-one grams of diethyl oxalate were condensed with 50 grams of ethyl propionate, in presence of sodium ethylate,³ on June 10, 1908. This salt was then allowed to stand exposed to the air, in an

¹ Johnson: *Loc. cit.*

² *Loc. cit.*

³ Arnold: *Loc. cit.*

open flask, until October 15, 1908. It was then condensed with pseudoethylthiourea in the usual manner, when we obtained 22 grams of pyrimidine melting at 209° – 214° (Experiment 6 in table).

Ethyl Ester of 2-Ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine,

$$\begin{array}{c}
 \text{NH}-\text{CO} \\
 | \qquad | \\
 \text{C}_2\text{H}_5\text{SC} \quad \text{CCH}_3 \\
 || \qquad || \\
 \text{N}-\text{CCOOC}_2\text{H}_5
 \end{array}$$

—The sodium salt of diethyl

oxalpropionate was prepared in the usual manner by condensing 71 grams of diethyl oxalate with 50 grams of ethyl propionate in presence of metallic sodium. This salt was then dissolved in 400–500 cc. of water and mixed with an aqueous solution containing 0.6 molecular proportion of pseudoethylthiourea. The mixture was then allowed to stand, at ordinary temperature, for several days, when 17.0 grams of the ethyl ester had separated. After concentrating the aqueous filtrate and then acidifying with hydrochloric acid, we obtained the corresponding acid. This ester is difficultly soluble in water but very soluble in boiling alcohol. It crystallizes from 95 per cent. alcohol in prisms which melt at 172° – 173° to a clear oil. It dissolves in sodium hydroxide solution without decomposition but on warming it easily undergoes saponification. The ester is also formed quantitatively by the action of ethyl iodide on the silver salt of 2-ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine. Analysis (Kjeldahl):

	Calculated for $\text{C}_{10}\text{H}_{14}\text{O}_8\text{N}_2\text{S}$.	Found.
N	11.56	11.8

Behavior of 2-Ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine on Heating.—A few grams of this mercaptopyrimidine (3–4 grams) were heated in an oil bath at 220° – 230° until effervescence ceased. A dark oil was obtained which solidified on cooling. This substance was purified by crystallization from hot water and separated in prisms melting at 159° . It was identified as 2-ethylmercapto-5-methyl-6-oxypyrimidine.¹ Analysis (Kjeldahl):

¹ Wheeler and Johnson: *Loc. cit.*

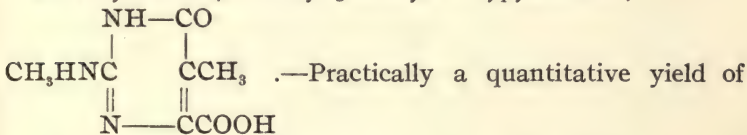
	Calculated for $C_7H_{10}ON_2S$.	Found.
N	16.47	16.6

Conversion of 2-Ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine into Thymine.—Sixteen grams of this mercapto-pyrimidine, melting at 218° – 220° , were heated in an oil bath at 220° – 230° until the evolution of carbon dioxide ceased (about 1.5 hours). We obtained 13.0 grams of crude 2-ethylmercapto-5-methyl-6-oxypyrimidine (theoretical yield is 12.7 grams), which was then digested for several hours with concentrated hydrochloric acid and converted into thymine. The acid solution was evaporated to dryness and the crude thymine decolorized in hot, aqueous solution with animal charcoal and then crystallized from water. It separated in colorless crystals, decomposing at about 325° – 335° . The yield was 8.0 grams, or about 85 per cent. of the theoretical. Since 36–37 grams of 2-ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine can be obtained from 50 grams of ethyl propionate (see table) this amount of thymine (8 grams) therefore corresponds to 21.6 grams of the ester.

A quantitative yield of thymine from 21.6 grams of ethyl propionate would be 26.5 grams. Analysis (Kjeldahl):

	Calculated for $C_5H_8O_2N_2$.	Found.
N	22.22	22.00

2-Methylamino-4-carboxyl-5-methyl-6-oxypyrimidine,



this pyrimidine was obtained when 7 grams of 2-ethylmercapto-4-carboxyl-5-methyl-6-oxypyrimidine and 9 grams of a 33 per cent. solution of methylamine were heated at 140° – 150° for 4 hours. It was precipitated from cold, aqueous solutions of its sodium, ammonium and methylamine salts by addition of acetic acid. It was very insoluble in cold water and crystallized from hot water in long, hairy crystals which melted

at 270° – 280° , according to the rate of heating, with effervescence. Analysis (Kjeldahl):

	Calculated for $C_7H_9O_3N_3$.	Found.
N	22.9	22.4

Methylamine Salt, $C_7H_9O_3N_3 \cdot CH_3NH_2$.—This salt crystallized from hot water in granular crystals, which decomposed with violent effervescence at 274° . Two of the crystals that were used for analysis weighed 0.0393 and 0.03170 gram, respectively. Analysis (Kjeldahl):

	Calculated for $C_7H_9O_3N_3 \cdot CH_3NH_2$.	Found.
N	26.1	25.91

Hydrochloride, $C_7H_9O_3N_3 \cdot HCl$.—This salt was prepared by dissolving the pyrimidine base in hot, dilute hydrochloric acid and allowing the solution to cool. The salt separated in prismatic crystals, which decomposed at 276° – 283° with effervescence. Analysis (Kjeldahl):

	Calculated for $C_7H_9O_3N_3 \cdot HCl$.	Found.
N	19.14	19.32

NEW HAVEN, CONN.,
June 1, 1909.

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[Contributions from the Sheffield Laboratory of Yale University.]

CLXXII.—RESEARCHES ON PYRIMIDINES:
THE ACTION OF METHYL IODIDE AND OF BENZYL
CHLORIDE UPON 2-OXY-4-METHYL-6-METHYL-
MERCAPTOPYRIMIDINE.²

[FORTY-SEVENTH PAPER.]

BY HENRY L. WHEELER AND DAVID F. MCFARLAND.

The papers so far published on the alkylation of mercaptopyrimidines, with but one exception, have been confined to a description of the results obtained from a study of 2-mer-

² Part of a thesis presented by David F. McFarland for the degree of Ph.D., Yale, 1909.

capto-6-oxypyrimidines. In most cases 2-mercapto-6-oxypyrimidines were found to alkylate both in the 1- and, more or less, in the 3-position.¹

In the exception mentioned, Wheeler and Johnson² showed that when a compound having the opposite configuration, the mercapto group and the oxygen atom being interchanged, 2-oxy-6-methylmercaptopyrimidine for example, was treated with potassium hydroxide and either methyl iodide or benzyl chloride, 3-alkyl derivatives were obtained. No 1-derivative was observed in this particular alkylation. Since the 3-alkyl-6-mercapto derivatives pass quantitatively into the 3-alkyl compounds of uracil when boiled with hydrochloric acid, this procedure is therefore the best for the preparation of these compounds.

With this result at hand, it then became a question whether or not 2-oxy-6-mercaptopyrimidines in other cases or in general would be the best to select for the preparation of 3-alkyl derivatives. Cytosine, or 2-oxy-6-aminopyrimidine, which has a constitution analogous to these 2-oxy-6-mercaptopyrimidines, also gives the 3-alkyl derivative on methylation.³

It seems to us that any new facts in regard to methods which lead to the formation of 3-alkyl derivatives or 3-attachments are of interest since results have been obtained by Johnson and Clapp⁴ which can be explained by the assumption that uracil, thymine, and cytosine are substituted or attached to other groups in these positions in the nucleic acids.

In our preceding paper we have shown that 2-methylmercapto- and 2-ethylmercapto-4-methyl-6-oxypyrimidine give 1-alkyl derivatives, the formation of the isomeric 3-derivatives in these cases not being observed. It was therefore of especial interest, in the above connection, to study, in this case, the alkylation of the compound having the opposite configuration, namely, 2-oxy-4-methyl-6-methylmercapto-

¹ For a list of these papers see *THIS JOURNAL*, **42**, 30 (1909).

² *Ibid.*

³ Johnson and Clapp: *J. Biol. Chem.*, **5**, 163 (1908).

⁴ *Loc. cit.*

pyrimidine. This has now been done and we find that this pyrimidine, with methyl iodide and benzyl chloride, not only gives 3-alkyl derivatives but also the isomeric 1-compounds. In the case of the action of methyl iodide, the 1- and 3-isomers are formed in about equal proportions. Benzyl chloride gave more of the 3- than of the 1-benzyl compound.

The presence of a mercapto group or the absence of oxygen in the 6-position therefore appears to favor the formation of 3-alkyl derivatives. There is, however, no strict regularity in these alkylations, so that in new cases it is impossible to predict whether a 1- or 3-derivative, or a mixture of both, will result.

The starting point for the present work was the preparation of List's¹ 2-thio-4-methyluracil (I) from acetoacetic ester and thiourea. This gave 2-methylmercapto-4-methyl-6-oxypyrimidine (II) by List's method of alkylation.

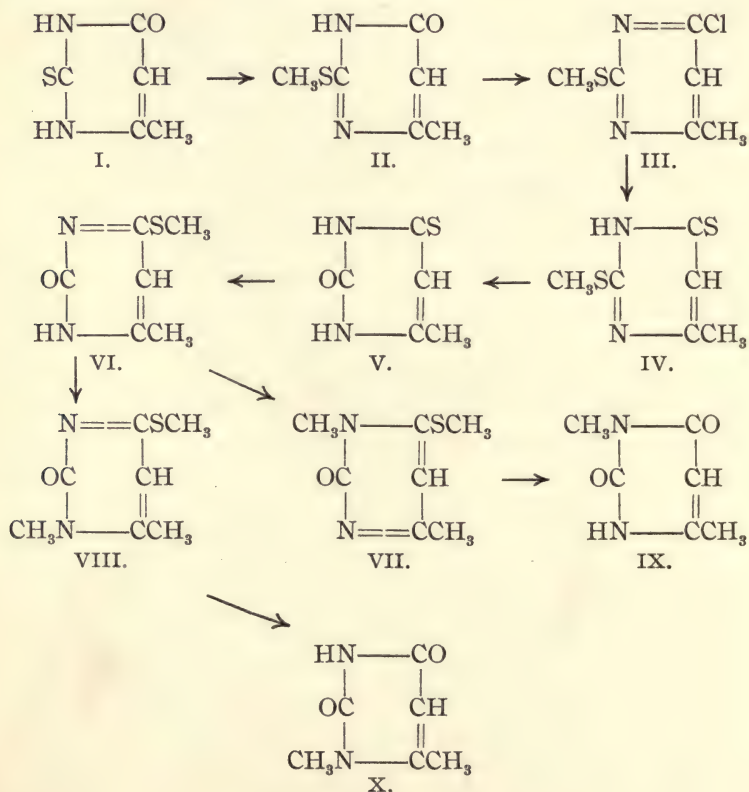
The new 2-methylmercapto-4-methyl-6-chlorpyrimidine (III) was then prepared by warming the material with phosphorus pentachloride and some oxychloride. When this compound was warmed with an excess of alcoholic potassium sulphhydrate, 2-methylmercapto-4-methyl-6-thiopyrimidine (IV) was obtained, and when the latter was boiled with hydrochloric acid 4-methyl-6-thiouracil (V) resulted.

The calculated quantity of sodium ethylate and methyl iodide then gave 2-oxy-4-methyl-6-methylmercaptopyrimidine (VI). An excess of potassium hydroxide and methyl iodide, in alcoholic solution, gave 2-oxy-3,4-dimethyl-6-methylmercaptopyrimidine (VIII) and 2-oxy-1,4-dimethyl-6-methylmercaptopyrimidine(?) (VII). The latter was not obtained in a state of purity but its presence in the oily fraction was indicated by the behavior of this fraction toward hydrochloric acid. When boiled with hydrochloric acid the compounds VII and VIII gave the corresponding dimethyluracils described by Behrend,² namely, 1,4-dimethyluracil (IX) and 3,4-dimethyluracil (X).

¹ Ann. Chem. (Liebig), **236**, 12 (1886).

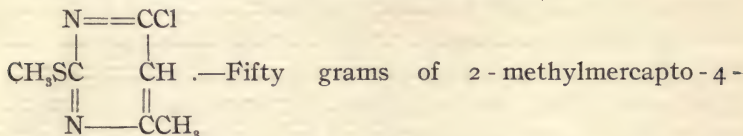
² Behrend and Dietrich: Ann. Chem. (Liebig), **309**, 265 (1899). Behrend and Thurn: *Ibid.*, **323**, 160 (1902).

The formation of 1-alkyl derivatives in this reaction could be explained otherwise, without the assumption of the formation of the compound represented by formula VII, if 2-oxy-4-methyl-6-methylmercaptopyrimidine lost mercaptan during the alkylation. 4-Methyluracil being formed, 1-alkyl derivatives would result. However, we have treated 2-oxy-4-methyl-6-methylmercaptopyrimidine with alkali, under the same conditions as those in the alkylations, and we have found that no 4-methyluracil was formed. The mercapto compound was recovered unaltered. The various steps in the synthesis of these pyrimidines may, therefore, be represented as follows:



EXPERIMENTAL PART.

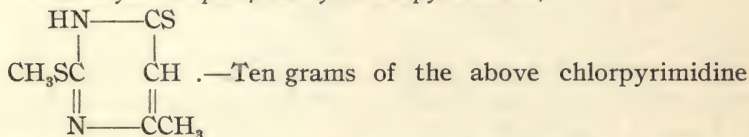
2-Methylmercapto-4-methyl-6-chlorpyrimidine,



methyl-6-oxypyrimidine were moistened with phosphorus oxychloride in a distilling bulb and then one molecular proportion (66.8 grams) of phosphorus pentachloride was added. No action was observed in the cold, and even when the mixture was warmed the reaction began only very slowly. The mass slowly liquefied with a regular, quiet evolution of hydrogen chloride. After two hours warming, the liquefaction was complete and the evolution of gas was greatly diminished. The phosphorus oxychloride was removed by distilling under reduced pressure, and the oil which remained was poured on cracked ice. It solidified to a yellow solid, which was allowed to remain in the ice water for some time and then extracted with ether. The solution was dried with calcium chloride and, on evaporation, the oil obtained was distilled at 32–35 mm. pressure. The greater part (42.8 grams) boiled steadily at 147°. This is 77 per cent. of the calculated. On cooling, this fraction solidified and then melted at 39°–40°. The substance is very soluble in all of the common solvents. When dissolved in the smallest possible quantity of petroleum ether it separated in beautiful, long needles. These were pressed on filter paper and dried in a desiccator for analysis:

	Calculated for $\text{C}_6\text{H}_7\text{N}_2\text{SCl}$.	Found.
N	16.02	16.02

2-Methylmercapto-4-methyl-6-thiopyrimidine,



were mixed with an alcoholic solution of potassium hydrosulphide, made by saturating a solution of 19.2 grams of potas-

sium hydroxide in 60 cc. of alcohol with hydrogen sulphide. The chlor compound dissolved and very soon crystals of the potassium salt of 2-methylmercapto-4-methyl-6-thiopyrimidine began to separate. The mixture was warmed for half an hour on the steam bath and the alcohol was then evaporated. The residue dissolved almost completely in water and the solution was filtered from a slight reddish sediment. On acidifying with dilute acetic acid, the free thio compound was precipitated. The quantity obtained (9.85 grams) agreed almost exactly with the theoretical yield. This substance is very difficultly soluble in boiling water, from which it separates in light yellow, minute needles. It dissolves easily in ammonium hydroxide and separates again when the ammonia is boiled off. It is unstable in aqueous alkali and the solution takes on a dark red color. Dilute alcohol or water should therefore not be used in its preparation. Alcohol dissolves it with some difficulty, giving needle-like prisms. On standing, the alcoholic mother liquors take on a deep red color.

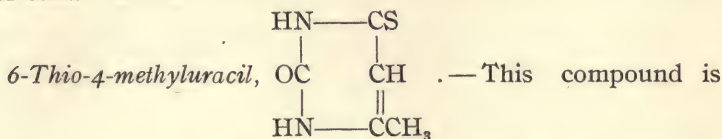
	Calculated for $C_6H_8N_2S_2$.	Found.
N	16.27	16.12

2-Methylmercapto-4-methyl-6-thiopyrimidine exhibited a characteristic behavior when heated, the product obtained at high temperatures being 2,6-dithio-4-methyluracil. This substance has been described by Gabriel and Colman.¹ When slowly heated, such as is commonly done in taking melting points, it partially melted, like a mixture, at 212° to a milky mass, which effervesced on further heating and then solidified. If the tube was placed in a bath already heated to 200° and the temperature rapidly raised, it then melted completely to a clear yellow oil at 214° . A slight elevation of temperature caused the oil to effervesce and finally solidify to a crystalline solid. On further heating this solid grew red, the color deepening until the material melted or decomposed to a red-brown oil at 280° – 290° .

One gram of the mercapto-6-thiopyrimidine was heated for

¹ Ber. d. chem. Ges., **32**, 2921 (1899).

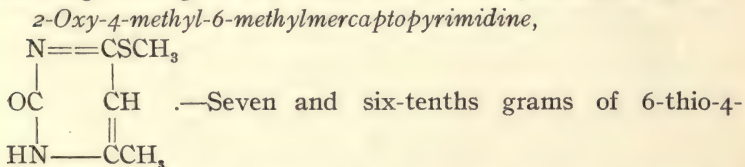
a short time at 215° – 223° . The product was treated with hot alcohol and the portion which did not dissolve was found to be also almost insoluble in boiling water. On heating, decomposition set in above 260° , but the material did not melt at 310° . A nitrogen determination gave 17.53 per cent. while the calculated for 2,6-dithio-4-methyluracil is 17.72 per cent.



formed quantitatively by boiling 2-methylmercapto-4-methyl-6-thiopyrimidine with strong hydrochloric acid for several hours and then evaporating to dryness. Long heating is required to completely expel the mercaptan from the compound. The product is almost insoluble in alcohol and difficultly soluble in boiling water. It crystallizes in irregular, prismatic forms, has a sulphur-yellow color, but no definite melting point. When heated it decomposes above 250° .

	Calculated for $\text{C}_6\text{H}_6\text{ON}_2\text{S}$.	Found.
N	19.71	19.42

The sulphur in this compound is more firmly bound than that in 6-thiouracil or 6-thiothymine. It was not removed on long heating on the steam bath with hydrochloric acid.



methyluracil were dissolved by warming with 2.2 grams of sodium hydroxide in 50 cc. of water and 30 cc. of methyl alcohol, and 8.5 grams of methyl iodide were added. The mixture was warmed until no further alkaline reaction was obtained. It was then evaporated to dryness. The product dissolved easily in water, leaving only a little oil, which was removed by filtration. On standing, pale yellow, flat, needle-

like crystals formed. The yield in one case was 83 per cent. of the calculated. When recrystallized from water the material melted at 174° – 175° to a clear oil. The substance was very soluble in water and alcohol, and it had a tendency to form supersaturated solutions. On this account it crystallized from water only after standing for some time. It is not appreciably volatile with steam.

	Calculated for $C_6H_8ON_2S$.	Found.
N	17.94	17.67

Action of Benzyl Chloride.—Four grams of 2-oxy-4-methyl-6-methylmercaptopyrimidine were dissolved in alcohol with 1.45 grams of potassium hydroxide. To the cooled solution, 3.3 grams of freshly distilled benzyl chloride were added and the mixture was allowed to stand for several days. The reaction then still being incomplete, the mixture was warmed for two hours on the steam bath. Some potassium chloride which separated was filtered off and the solution was allowed to evaporate spontaneously. A small amount of solid remained, mixed with a larger quantity of red oil, which had a very pungent odor. When the mixture was spread on a porous plate the oil was absorbed, leaving 1.6 grams of the sticky solid. This was very soluble in alcohol and benzene and very difficultly soluble in water. From none of these solutions could a pure crystalline substance be obtained, so the crude solid was treated directly with hydrochloric acid.

One and a half grams of the solid were digested on the steam bath with a large excess of concentrated hydrochloric acid and then evaporated to dryness. This operation was twice repeated before mercaptan was completely eliminated. The residue weighed 1.1 grams. On crystallizing from alcohol it was found to consist principally of 4-methyluracil, decomposing at 265° – 300° , and, by extracting the product with cold chloroform a very small amount of 1-benzyl-4-methyluracil was obtained. The red oil, which was absorbed in a porous plate, was extracted with boiling alcohol and treated with concentrated hydrochloric acid as above. When mer-

captan ceased being evolved, the dry residue was stirred with alcohol. This left 1.1 grams of substance undissolved, while the red color of the residue was removed. When the material was crystallized once from alcohol, Hagen's 3-benzyl-4-methyluracil, melting at 231° – 232° , was obtained. The mother liquor appeared to contain a mixture of this compound and of the 1-benzyl derivative. We conclude from the above that of the two isomers the 3-benzyl derivative is formed in larger amount.

Action of Methyl Iodide; 2-Oxy-3,4-dimethyl-6-methylmercaptopyrimidine.—Four and three-tenths grams of potassium hydroxide were dissolved in 50 cc. of methyl alcohol and 4 grams of 2-oxy-4-methyl-6-methylmercaptopyrimidine were added. This dissolved at once without warming. Three molecular proportions (11 grams) of methyl iodide were then added and the mixture was allowed to stand two days. At the end of this time considerable potassium iodide had separated and the solution no longer gave an alkaline reaction. The alcohol was then evaporated under reduced pressure and the dry residue was extracted with three portions of boiling chloroform. On evaporation of the chloroform at ordinary temperatures, slightly yellow, large, prismatic crystals mixed with oil separated. The oil did not solidify on standing for some time. It was removed by absorption in filter paper and saved for later treatment (see below).

The crystals, which weighed 2.3 grams or 53 per cent. of the calculated for dimethyl-6-methylmercaptopyrimidine, were twice recrystallized from benzene. Some brownish color was removed by boiling the solution with animal charcoal, whereupon, on filtering, splendid prisms, somewhat irregular in outline, were obtained. They melted to a clear oil at 170° – 171° , and were found to be very soluble in water and in alcohol, but only moderately so in benzene.

	Calculated for $C_7H_{10}ON_2S$.	Found.
N	16.47	16.53

This material was boiled with hydrochloric acid until it gave no test for sulphur. It was then crystallized twice from alcohol, whereupon it melted at 220° and agreed in proper-

ties with Behrend's 3,4-dimethyluracil. A nitrogen determination gave 20.06 per cent. nitrogen while the calculated for this compound is 20.00 per cent.

1,4-Dimethyl-2-oxy-6-methylmercaptopyrimidine (?).—This compound was not isolated in a pure state but its presence in the oil obtained above was indicated by the hydrolysis of the oil with strong hydrochloric acid. After digesting on the steam bath until mercaptan was no longer evolved, the solution was evaporated to dryness and the residue was crystallized from water. It separated in small prisms melting sharply, to a clear brown oil, at 260° and when mixed with a sample of β -dimethyluracil or 1,4-dimethyluracil the melting point was not lowered.

	Calculated for $C_6H_8O_2N_2$.	Found.
N	20.00	20.02

2-Oxy-4-methyl-6-orthonitrobenzylmercaptopyrimidine.—Molecular proportions of 6-thio-4-methyluracil, potassium hydroxide, and *o*-nitrobenzyl chloride were mixed in dilute alcoholic solution. The mixture was then warmed until it gave a neutral reaction. When the alcohol was evaporated and the residue was treated with water the yield of crude product agreed with the calculated amount. This material dissolved fairly easily in hot alcohol and, on cooling, it gave clusters of yellow, lancet-shaped crystals melting to a clear oil at 205° .

	Calculated for $C_{12}H_{11}O_3N_3S$.	Found.
N	15.16	15.24

2-Oxy-4-methyl-6-metadinitrophenylmercaptopyrimidine, prepared in a similar manner to the above, from 6-thio-4-methyluracil, potassium hydroxide, and 1-brom-2,4-dinitrobenzene, formed very small bunches of fine, mustard-yellow needles when crystallized from alcohol. It melted at 208° .

	Calculated for $C_{11}H_8O_6N_4S$.	Found.
N	18.18	18.05

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[Contributions from the Sheffield Laboratory of Yale University.]

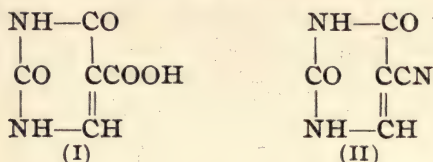
CLXXV.—RESEARCHES ON PYRIMIDINES:
SYNTHESIS OF 5-CYANURACIL.

[FORTY-EIGHTH PAPER.]

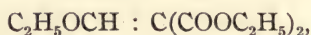
By TREAT B. JOHNSON.

The present work was undertaken with the object of preparing some pyrimidines to be used for the syntheses of new

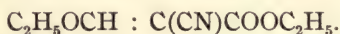
derivatives of thymine. I shall describe the preparation and properties of the nitrile of uracil-5-carboxylic acid (I), *viz.*, 5-cyanuracil (II), and some of its derivatives.



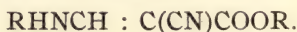
It has been shown in a previous paper from this laboratory¹ that diethyl ethoxymethylenemalonate,²



condenses smoothly with pseudothiureas, $\text{H}_2\text{NC}(\text{SR}) : \text{NH}$, in aqueous solution, in the presence of alkali, giving 2-alkyl-mercapto-5-carboxyl-6-oxypyrimidines. Uracil-5-carboxylic acid (I) is then obtained easily by hydrolysis of these mercaptopyrimidines with acids. It seemed very probable to the writer that 5-cyanuracil (II) might be synthesized in an analogous manner from ethyl ethoxymethylenecyanacetate,



DeBollemont³ has described several esters of this character, which he has prepared by condensation of orthoformic esters, $\text{CH}(\text{OR})_3$, with esters of cyanacetic acid in presence of acetic anhydride. He has also examined the behavior of several of them towards organic bases and shown that they react smoothly with formation of the corresponding amino derivatives,



The action of ureas, thiureas, pseudoureas, and pseudothiureas on these esters, however, has not been investigated.

Ethyl ethoxymethylenecyanacetate was prepared for my experiments according to the directions of deBollemont.⁴ I now find that pseudoethylthiurea condenses in alcoholic

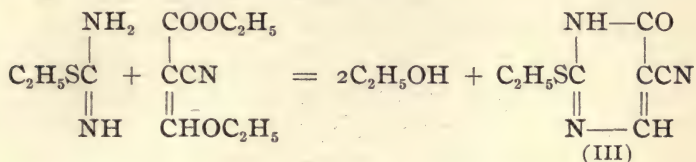
¹ THIS JOURNAL, **37**, 392 (1907).

² Claisen: Ann. Chem. (Liebig), **297**, 75 (1897).

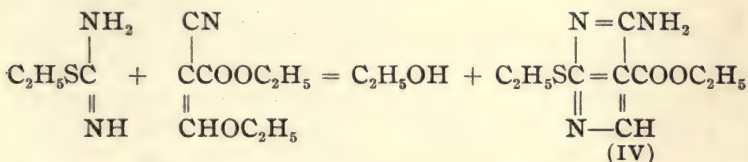
³ Compt. Rend., **128**, 1338; **129**, 5; Bull. Soc. Chim., [3] **25**, 18, 28, 39.

⁴ Loc. cit.

solution with this ester, in the presence of alkali, in two ways, giving a mixture of two mercaptopyrimidines. The main reaction is a condensation with the ester, similar to that with diethyl ethoxymethylenemalonate,¹ giving 2-ethyl-mercapto-5-cyan-6-oxypyrimidine (III). This condensation is represented by the following equation:



A part of the acrylic ester, however, reacts with the pseudothiourea, giving 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine (IV), which has previously been described in a paper from this laboratory.²



This interesting observation suggests that other cyanides containing the grouping $\text{C}_2\text{H}_5\text{OCH} : \text{C} - \text{CN}$ will be found to condense with pseudothioureas, giving aminopyrimidines.

It is interesting to note here that ethyl acetylcyanacetate,



does not condense with pseudoethylthiourea to give a pyrimidine.³ On the other hand, it has been shown that the pseudoureas,⁴ $\text{H}_2\text{NC}(\text{OR}) : \text{NH}$, condense with ethyl cyanacetate, in presence of alkali, giving the corresponding 2-alkyloxy-4-amino-6-oxypyrimidines.⁵

¹ *Loc. cit.*

² Wheeler and Johns: *THIS JOURNAL*, **38**, 594.

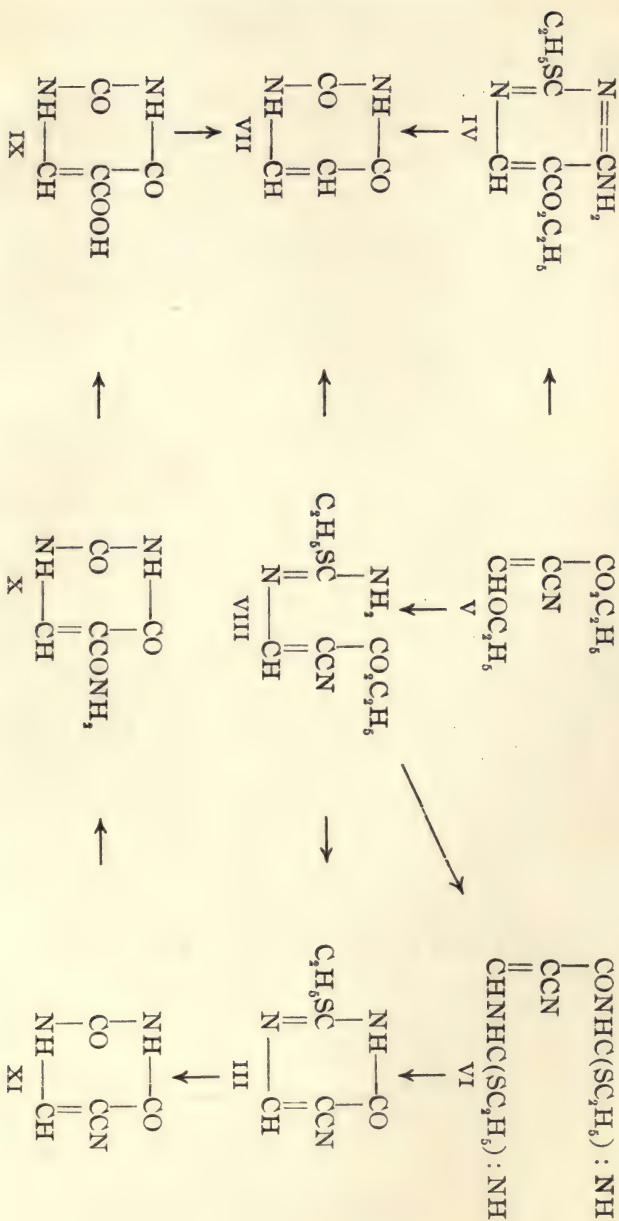
³ Wheeler: *THIS JOURNAL*, **28**, 358.

⁴ Stieglitz and McKee: *Ber. d. chem. Ges.*, **32**, 1494; **33**, 807, 1517; Stieglitz and Noble: *Ibid.*, **38**, 2243.

⁵ *Centrabl.*, **1904**, II, 631.

I also investigated the action of pseudoethylthiourea on ethyl ethoxymethylenecyanacetate (V) in alcohol containing no free alkali. When they were allowed to react under these conditions in molecular proportions, there was no evidence of the formation of 2-ethylmercapto-5-cyan-6-oxypyrimidine (III), and 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine (IV) and ethyl α -cyan- β -pseudoethylthiourea-acrylate (VIII) were the only products of the reaction. If more than one molecular proportion of pseudoethylthiourea is used for the condensation the ethyl α -cyan- β -pseudoethylthiourea-acrylate that is formed then reacts with the excess of pseudothiourea, giving α -cyan- β -pseudoethylthiourea-acrylpseudoethylthiourea (VI).

Ethyl α -cyan- β -pseudoethylthiourea-acrylate (VIII) and α -cyan- β -pseudoethylthiourea-acrylpseudoethylthiourea (VI) are both converted quantitatively into 2-ethylmercapto-5-cyan-6-oxypyrimidine (III) when warmed with alkali. A quantitative yield of 5-cyanuracil (XI) is then obtained by hydrolysis of this mercaptopyrimidine, in alcohol, with sulphuric acid. Attempts to hydrolyze this mercaptopyrimidine (III) smoothly to 5-cyanuracil, in aqueous solution, were unsuccessful. The nitrile group slowly undergoes hydrolysis under these conditions, giving a mixture of 5-cyanuracil (XI) and uracil-5-carboxamide (X). These are both converted quantitatively into uracil-5-carboxylic acid (IX) and finally into uracil (VII) by long digestion with concentrated hydrochloric acid. These various transformations are represented by the following formulas:

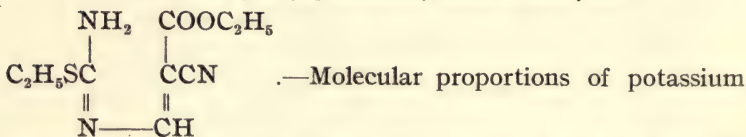


EXPERIMENTAL PART.

Ethyl Ethoxymethylenecyanacetate,
 $C_2H_5OCH : C(CN)COOC_2H_5$.—This ester was prepared according to the directions given by de Bollemont.¹ It melts at 52° – 53° and is insoluble in water but very soluble in alcohol, ether, and benzene.

Condensation of Ethyl Ethoxymethylenecyanacetate with One Molecular Proportion of Pseudoethylthiourea in Alcohol.

Ethyl α -Cyan- β -pseudoethylthiourea-acrylate,

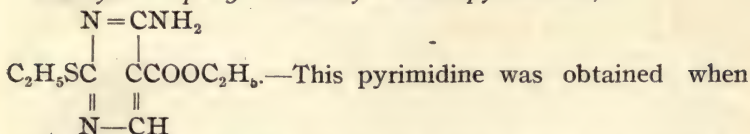


hydroxide (0.45 gram) and the hydrobromide of pseudoethylthiourea (1.4 grams) were dissolved separately in 7 cc. of 95 per cent. alcohol, the solutions cooled to 0° , and combined. The undissolved potassium bromide was then separated quickly by filtration and 1.2 grams of ethyl ethoxymethylenecyanacetate added to the cold alcohol solution of pseudothiourea. The ester dissolved at once and within 1–2 minutes a yellow, crystalline substance separated. After standing a few minutes this was filtered off, washed thoroughly with ether, and the ether washings saved (see below). The substance obtained here, insoluble in ether, was the ethyl acrylate represented above and melted without further purification at 120° – 125° . The ester is soluble in alcohol, insoluble in cold water and ether, and crystallizes from benzene in tufts of yellow distorted needles melting at 130° with slight effervescence. It separates from a hot aqueous solution as an oil, which finally crystallizes in colorless needles melting at the same temperature. Nitrogen (Kjeldahl):

	Calculated for $C_9H_{13}O_2N_2S$.	Found.
N	18.50	18.7

¹ *Loc. cit.*

2-Ethylmercapto-5-carbethoxy-6-aminopyrimidine,



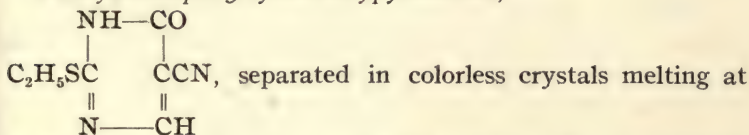
—This pyrimidine was obtained when the ether solution described above was allowed to evaporate. It was insoluble in cold, dilute sodium hydroxide solution but soluble in hydrochloric acid, and crystallized from 95 per cent. alcohol in rectangular plates melting at 102° – 103° to a clear oil with no effervescence. This same pyrimidine has previously been described by Wheeler and Johns.¹ A mixture of my derivative and their pyrimidine melted at 102° . Nitrogen (Kjeldahl):

	Calculated for $\text{C}_9\text{H}_{13}\text{O}_2\text{N}_3\text{S}$.	Found.
N	18.50	18.6

The comparative yields of the above acrylic ester and this 6-aminopyrimidine were irregular, but the ester was always the chief product of the reaction. They were apparently the only compounds formed under the conditions employed.

Action of Alkali on Ethyl α -Cyan- β -pseudoethylthioureacacrylate.—This ester is not decomposed by cold, dilute sodium hydroxide solution. On the other hand, when warmed with alkali it immediately dissolved, giving the sodium salt of 2-ethylmercapto-5-cyan-6-oxypyrimidine. When the alkaline solution was acidified with hydrochloric acid,

2-Ethylmercapto-5-cyan-6-oxypyrimidine,



separated in colorless crystals melting at 218° – 20° to an oil. It crystallizes from hot water in prisms, which melt at 222° to a clear oil without effervescence. The pyrimidine gives a strong test for uracil when treated with bromine water and barium hydroxide solution.² Nitrogen determinations (Kjeldahl):

¹ *Loc. cit.*

² Wheeler and Johnson: *J. Biol. Chem.*, **3**, 183 (1907).

	Calculated for $C_7H_7ON_3S$.	I.	Found.	II.
N	23.22	23.0		23.15

This pyrimidine and 2-ethylmercapto-5-carbethoxy-6-amino-pyrimidine are the only products of the reaction when pseudoethylthiourea is condensed with ethyl ethoxymethylenecyanacetate in alcohol in the presence of an excess of alkali.

Condensation of Ethyl Ethoxymethylenecyanacetate with More than One Molecular Proportion of Pseudoethylthiourea in Alcohol.

An alcoholic solution of pseudoethylthiourea was prepared by dissolving 20 grams of the hydrobromide of pseudoethylthiourea (1.7 mols.) in 70 cc. of absolute alcohol and then adding, at 0° , a solution of 6.1 grams of potassium hydroxide (1.7 mols.) in 30 cc. of 95 per cent. alcohol. After filtering from potassium bromide, 10.7 grams of ethyl ethoxymethylenecyanacetate (1 mol.) were added to the pseudourea solution at once when there was an immediate reaction and a thick mush of crystalline material was obtained. A portion of this material was filtered off and washed with ether. It then melted at 128° – 130° . This insoluble substance was identified as ethyl α -cyan- β -pseudoethylthiourea-acrylate, which was obtained in my previous condensation (see above). On evaporating the ether solution I obtained 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine¹ which was identified by its melting point, 102° – 103° .

The main portion of the reaction mixture, however, was allowed to stand, at ordinary temperature, for about 2–3 hours, when, to my surprise, practically all of the acrylic ester, with the exception of about 1–2 grams, had dissolved. The solution was then filtered, concentrated on the steam bath, and cooled when I obtained about 12–13 grams of crystalline material. This was washed with ether to remove any 2-ethylmercapto-5-carbethoxy-6-aminopyrimidine, and then triturated with cold, dilute sodium hydroxide solution. I obtained 10.5 grams of a crystalline substance insoluble in the alkaline solution. It

¹ Wheeler and Johns: *Loc. cit.*

was soluble in hot water and alcohol and crystallized from hot water in well-developed prisms which melted at 164° – 165° with effervescence. A nitrogen determination agreed with the calculated value for α -cyan- β -pseudoethylthiourea-acrylpseudoethylthiourea, $\text{NH}_2\text{C}(\text{SC}_2\text{H}_5) : \text{NCH} : \text{C}(\text{CN})\text{CO.N} : \text{C}(\text{SC}_2\text{H}_5)\text{NH}_2$.

	Calculated for $\text{C}_{10}\text{H}_{15}\text{ON}_5\text{S}_2$.	Found.
N	24.56	24.43

When the sodium hydroxide solution (above) was carefully acidified with hydrochloric acid, 2-ethylmercapto-5-cyan-6-oxypyrimidine separated. It crystallized in prisms melting at 222° to an oil. Analysis (Kjeldahl):

	Calculated for $\text{C}_7\text{H}_7\text{ON}_3\text{S}$.	Found.
N	23.22	23.0

Action of Alkali on α -Cyan- β -pseudoethylthiourea-acrylpseudoethylthiourea.

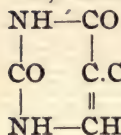
About 1.5 grams of this compound were warmed with 10 cc. of a 10 per cent. aqueous solution of sodium hydroxide for a few minutes. Ethyl mercaptan was evolved and the compound dissolved, giving a clear solution. When this was acidified with hydrochloric acid 2-ethylmercapto-5-cyan-6-oxypyrimidine separated in prisms melting at 220° – 222° . Analysis (Kjeldahl):

	Calculated for $\text{C}_7\text{H}_7\text{ON}_3\text{S}$.	Found.
N	23.22	23.16

Behavior with Hydrochloric Acid.—One gram of α -cyan- β -pseudoethylthiourea-acrylpseudoethylthiourea was dissolved in about 40–50 cc. of concentrated hydrochloric acid and the solution evaporated to dryness. I obtained practically a quantitative yield of 5-cyanuracil (see below) which melted without purification at 291° – 293° . After one crystallization from water it melted at 293° – 295° and a nitrogen determination (Kjeldahl) gave:

	Calculated for $\text{C}_5\text{H}_3\text{O}_2\text{N}_3$.	Found.
N	30.6	30.2

2,6-Dioxy-5-cyanpyrimidine (5-Cyanuracil),



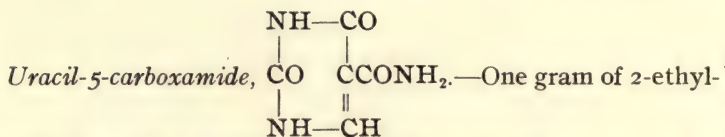
—A quantitative yield of this pyrimidine was also

obtained by hydrolysis of 2-ethylmercapto-5-cyan-6-oxypyrimidine with sulphuric acid as follows: 0.7 gram of the mercaptopyrimidine was dissolved in a mixture of 30 cc. of alcohol and 3 cc. of concentrated sulphuric acid and the solution boiled until the evolution of ethyl mercaptan ceased. The 5-cyanpyrimidine separated in hard, granular crystals melting at 291° – 292° . It is difficultly soluble in cold alcohol and crystallizes from hot water in prisms which melt at 295° with decomposition. Analysis (Kjeldahl):

	Calculated for $\text{C}_5\text{H}_3\text{O}_2\text{N}_3$.	I.	Found.
N	30.6	30.1	30.55

When this pyrimidine was digested with concentrated hydrochloric acid for several hours it was converted quantitatively into uracil. Analysis (Kjeldahl):

	Calculated for $\text{C}_4\text{H}_4\text{O}_2\text{N}_2$.	Found.
N	25.00	24.6



mercapto-5-cyan-6-oxypyrimidine was dissolved in 50 cc. of concentrated hydrochloric acid and the solution evaporated to dryness on the steam bath. The crystalline material which was obtained was then dissolved in hot water and the solution cooled slowly, when this pyrimidine separated in small prisms. It is difficultly soluble in cold water and does not melt below 300° . It gives a strong test for uracil when treated with bromine water and barium hydroxide. After heating for 5 hours at 100° – 110° a nitrogen determination (Kjeldahl) gave:

	Calculated for $\text{C}_5\text{H}_5\text{O}_3\text{N}_3$.	Found.
N	27.00	26.80

This amide was converted quantitatively into uracil when digested with concentrated hydrochloric acid.

The aqueous mother liquor (above), after being filtered from uracil-5-carboxamide, was concentrated to a small volume and cooled, when the characteristic prisms of 5-cyanuracil separated. After two crystallizations from hot water it melted at 293° – 295° . Analysis (Kjeldahl):

	Calculated for $C_5H_3O_2N_3$.	Found.
N	30.6	30.1

NEW HAVEN, CONN.,
July, 1909.



[Contributions from the Sheffield Laboratory of Yale University.]

CLXXVII.—RESEARCHES ON PYRIMIDINES:
THE THIO DERIVATIVES OF THYMINE AND THE
PREPARATION OF THYMINE.¹

[FORTY-NINTH PAPER.]

BY HENRY L. WHEELER AND DAVID F. MCFARLAND.

In preparing uracil from ethylpseudothiourea hydrobromide and the sodium salt of ethyl formylacetate,² for some unknown reason it has sometimes happened that the yield obtained was very poor. A more satisfactory result was invariably obtained when sodiumformylacetate and thiourea were used.³ The employment of thiourea instead of the pseudothiourea had the additional advantage of being a more direct process. It rendered unnecessary the preparation of the pseudothiourea and was therefore less expensive, and, perhaps better than all, the presence of mercaptan was avoided.

These results suggested that the preparation of thymine might be improved in a similar manner. When the sodium salt of ethyl formylpropionate was condensed with thiourea in aqueous solution (four experiments) we were surprised to find that the yield of 2-thiothymine (I) was invariably about one-half what would be expected from the pseudothiourea condensation under similar conditions. Obviously this was no improvement over our original method.

We have recently found, in other cases, that certain β -ketone esters condense with thiourea in alcoholic solution when they

¹ Part of a thesis presented by David F. McFarland for the degree of Ph.D., Yale, 1909.

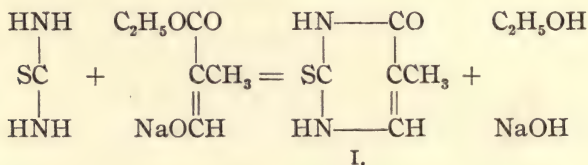
² Wheeler and Merriam: *THIS JOURNAL*, **29**, 478 (1903).

³ Wheeler and Liddle: *Ibid.*, **40**, 547 (1908).

failed to do so in water. The condensation of ethyl sodium-formylpropionate with thiourea was therefore carried out in alcoholic solution (eight experiments). This brought about the desired improvement. The yields were over twice those obtained in the aqueous condensation.

For comparison with our original method ethyl sodium-formylpropionate was condensed with ethylpseudothiourea in aqueous (four experiments) and alcoholic (one experiment) solutions. It was then found that the average yield of 2-ethyl-mercapto-5-methyl-6-oxypyrimidine, in these experiments, when expressed in the equivalent weight of thymine, was nearly identical (20.9 per cent. of the calculated) with that calculated from the average yield of 2-thiothymine obtained in the alcoholic condensations (22.6 per cent. of the calculated).

In other words, almost the same amount of thymine is obtained in these condensations whether we use thiourea in alcohol or pseudothiourea in water or alcohol. The use of thiourea, however, gives a little better yield and it is also to be recommended for the reasons stated above. The condensation takes place as follows:



It is peculiar that a similar condensation failed to take place in the case of urea and ethyl sodiumformylpropionate or ethyl sodiumformylacetate¹ in either absolute alcohol or aqueous solutions.

2-Thiothymine (I), like 2-thiouracil, is desulphurized and quantitatively converted into thymine (V) by simply dissolving in water and evaporating to dryness with a slight excess of chloracetic acid. The thymine prepared in this manner

¹ Wheeler and Liddle: *Loc. cit.*

melts higher and appears to be more readily purified than when prepared by means of a pseudothiourea.

We have prepared 6-thiothymine (II) and 2,6-dithiothymine (IV) in a manner similar to that used in the case of the corresponding uracil¹ and 4-methyluracil derivatives.² The preparation of the 6-thio derivatives in the thymine series is far less satisfactory than in the case of those previously described. The 2-ethylmercapto-5-methyl-6-thiopyrimidine (III), on boiling with hydrochloric acid, evolves mercaptan less easily than in the previous cases and the sulphur in the 6-position is also more or less removed at the same time, so that the yield is poor, or nothing but thymine is obtained. A similar behavior was observed in the preparation of 6-thiouracil but only on long warming with acid. On the other hand, 6-thio-4-methyluracil evolved mercaptan smoothly without being desulphurized in the 6-position.

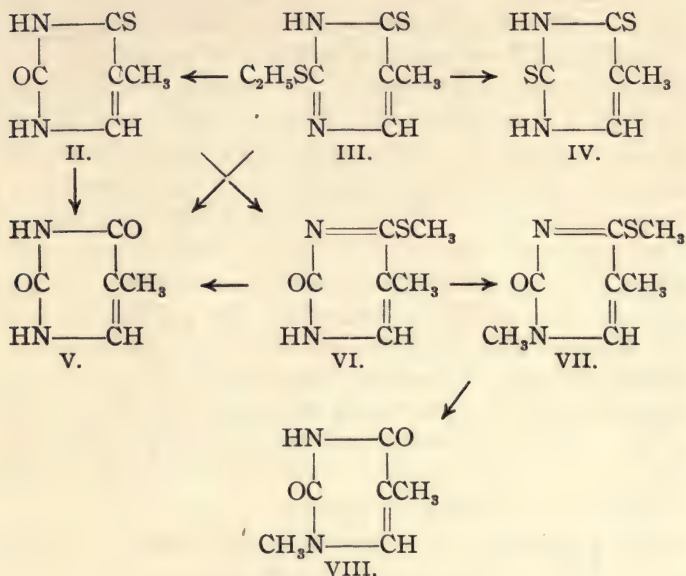
2,6-Dithiothymine (IV) was prepared from 2-ethylmercapto-5-methyl-6-thiopyrimidine (III) by heating with dry hydrogen chloride.

We have found that the methylation of 6-thiothymine first gives 2-oxy-5-methyl-6-methylmercaptopyrimidine (VI), as would be expected, and on further methylation this compound yields the 3-methyl derivative, 2-oxy-3,5-dimethyl-6-methylmercaptopyrimidine (VII). This result is in accordance with the general tendency, previously observed by us, of a 6-mercapto-2-oxypyrimidine to alkylate in the 3-position.

2-Oxy-3,5-dimethyl-6-methylmercaptopyrimidine (VII), on boiling with hydrochloric acid, gives a quantitative yield of 3-methylthymine (VIII). These compounds and their transformations may be represented as follows:

¹ Wheeler and Liddle: *Loc. cit.*

² Wheeler and McFarland: *THIS JOURNAL*, **42**, 431 (1909).



EXPERIMENTAL PART.

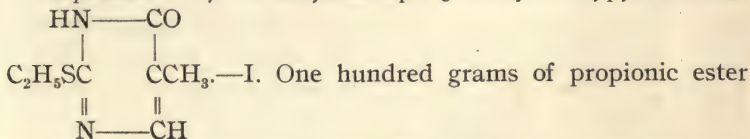
Ethyl Sodiumformylpropionate, $\text{NaOCH}=\text{C}(\text{CH}_3)\text{CO}_2\text{C}_2\text{H}_5$.—This salt was prepared, as Wislicenus directs,¹ in a manner similar to that used in the case of ethyl sodiumformylacetate. We have obtained the best results in the preparation of these salts when one atomic proportion of sodium was covered with dry ether in a flask attached to a return condenser and the mixture of esters slowly added. An excess of ethyl formate was employed and the amount of ether was sufficient to prevent the mixture from becoming thick. Three or four times the volume of the mixed esters was usually sufficient. If evaporation of the ether took place, owing to the esters being added too rapidly, or if not enough was present, the product frequently was sticky and difficult or impossible to filter. It therefore could not be washed with ether and dried satisfactorily. When 100 to 150 grams of each ester were used about a day and a half or two days was taken to add the mixture to the sodium. The sodium disappeared and the reaction was complete in about four days altogether.

In one experiment from 150 grams of ethyl propionate and

900 cc. of ether with one atomic proportion of sodium and 150 grams of ethyl formate, 145 grams of dry sodium salt were obtained. In the ether filtrate 9.6 grams of 2-thiothymine were found, or an equivalent of 32.3 grams more of sodium salt (see experiment XIV below). The total yield of crude sodium salt was therefore 177.3 grams for 150 grams of ethyl propionate, or 118.2 grams for 100 grams of ester.

In another experiment which was carried out in the same manner as the above, 50 grams of ethyl propionate gave 43.2 grams of dry sodium salt and an amount of 2-thiothymine (4.3 grams) in the ether filtrate (experiment XV) equivalent to 16.8 grams more of salt, making a total of 60 grams or 120 grams for 100 grams of ethyl propionate. This is 79 per cent. of the calculated. (See also experiment XIII below.) In the condensations in which we have used this crude salt, the yields of pyrimidine derivatives have in no case amounted to much over 30 per cent. of the calculated. The salt is obviously not pure, but whether or not this fact alone accounts for the low yield, or whether stereochemically different salts exist here, one form condensing and the other not, will have to be determined later.

Preparation of 2-Ethylmercapto-5-methyl-6-oxypyrimidine,¹



and 80 grams of formic ester were added to 22.5 grams of sodium covered with ether. The ethyl sodiumformylpropionate was not filtered off but was condensed with 100 grams of pseudoethylthiourea hydrobromide by means of 65 grams of potassium hydroxide in about 750 cc. of water. On acidifying with acetic acid, after warming the mixture, 33 grams of 2-ethylmercapto-5-methyl-6-oxypyrimidine melting at 150° were obtained.

II. In another experiment 150 grams of propionic ester, 120 grams of formic ester and 33.7 grams of sodium were used. The product was mixed with a solution of 150 grams of ethylpseudothiourea hydrobromide and 97 grams of potas-

¹ See Wheeler and Johnson: *THIS JOURNAL*, **31**, 595 (1904).

suim hydroxide in about a liter of water. The yield of mercaptopyrimidine was 57.5 grams.

III. This experiment was carried out by Dr. Victor C. Myers. One hundred and fifteen grams of propionic ester, 100 grams formic ester and 26 grams of sodium in 250 cc. of ether were taken. The sodium salt was not filtered off but was condensed with 97 grams of ethylpseudothiurea hydrobromide and 30 grams of potassium hydroxide. The solution was allowed to stand for 24 hours and then concentrated to one-half volume (300 cc.?) before precipitating with dilute acetic acid. The precipitate weighed 61.5 grams. This probably contained some potassium and sodium salts since on recrystallizing from water 40 grams of material melting at 158° – 159° was obtained.

IV. The above experiment was repeated with the same quantities and under the same conditions. The first portion of mercapto compounds separated weighed 53.3 grams. When recrystallized from water 38.3 grams of pure material were obtained. The mother liquor contained sodium and potassium salts.

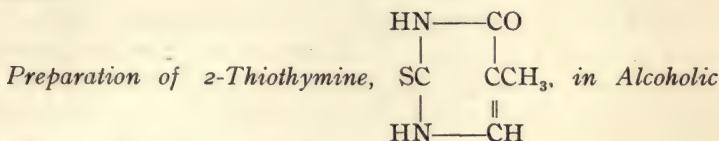
V. In this experiment the condensation was tried in alcohol. Thirteen and a half grams of dry ethyl sodiumformylpropionate were mixed with 16.4 grams of ethylpseudothiurea hydrobromide in 300 cc. of absolute alcohol in which 2.0 grams of sodium had been dissolved. Complete solution did not take place. The mixture was shaken and let stand for 20 hours, then warmed on the steam bath, evaporated to dryness and dissolved in 60 cc. of water and precipitated with acetic acid. The precipitate weighed 3.85 grams.

The following table gives a further comparison of the above results:

	Weight of ethyl propionate.	Weight of ethyl sodiumformylpropionate.	Weight of mercapto derivative obtained.	Calculated weight of mercapto derivative per 100 grams ester.	Per cent. yield of mercapto derivative.	Calculated weight of thymine from 100 grams ester.
I	100	120 ¹	33.0	33.0	19.75	24.4
II	150	180 ¹	57.5	38.3	22.9	28.4
III	115	138 ¹	61.5	53.3	31.9	39.5
IV	115	138 ¹	53.2	46.3	27.7	34.3
V	...	13.5	3.85	33.7	20.2	24.9

¹ Calculated from average yield of salt.

If we exclude experiments III and IV, in which the results are a little too high, as already stated, the average yield of thymine is 25.9 grams from 100 grams of ethyl propionate (or including these results it is 30.3 grams). Twenty-five and nine-tenths grams of thymine is 20.9 per cent. of the theoretical amount calculated directly from the ethyl propionate.



Solution.—VI. Nineteen grams of ethyl sodiumformylpropionate, pressed on paper and dried until all odor of ether had disappeared, were added to a solution of 9.5 grams (one molecule) of thiourea and 2.9 grams of sodium in 350 cc. of absolute alcohol. The mixture was warmed for 3 hours, evaporated to dryness, dissolved in 80 cc. of water and precipitated with dilute acetic acid. The crystalline precipitate weighed 6.8 grams.

VII. Twenty-eight grams of the sodium salt were warmed for five hours with 14 grams (1 molecule) of thiourea in 400 cc. of absolute alcohol, then evaporated to dryness, dissolved in water and precipitated with acetic acid. The yield in this case was 8.0 grams.

VIII. Fourteen and one-tenth grams of the dry sodium salt were treated with the same relative proportions of the thiourea, sodium ethylate, and alcohol and under the same conditions as in experiment VI. The yield of 2-thiothymine was 3.4 grams.

IX. Fifteen grams of the sodium salt, 4 grams of thiourea (about one-half molecule) and 2.2 grams of sodium dissolved in 150 cc. of absolute alcohol were mixed and heated for 3 hours. Then 25 cc. of water were added and the whole evaporated to dryness. The residue was taken up in 60 cc. of water and precipitated with acetic acid. The precipitate weighed 4.0 grams. On recrystallizing from 17.5 cc. of alcohol 3.4 grams separated.

X. Twenty-seven grams of the sodium salt were warmed with 13.5 grams (one molecule) of thiourea and 4.3 grams of sodium in 350 cc. of 95 per cent. alcohol for three and a half hours. There remained considerable material undissolved. The alcohol was evaporated and the residue was dissolved in 140 cc. of water. The addition of acetic acid to this solution gave 8.0 grams of 2-thiothymine.

XI. Thirteen and two-tenths grams of sodium salt were warmed with 3.5 grams of thiourea (a little over one-half molecule) and 2 grams of sodium in 150 cc. of 95 per cent. alcohol for 3 hours. Twenty-five cc. of water were added and the solution was warmed for a half hour, then evaporated to dryness. The residue was taken up in 60 cc. of water and precipitated, whereupon 3.3 grams of 2-thiothymine were obtained.

XII. Fifteen grams of dry sodium salt were warmed 3 hours with 4 grams of thiourea (one-half molecule + 0.5 gram) and 2.3 grams of sodium dissolved in 100 cc. of 85 per cent. alcohol. The sodium salt was first dissolved in 15 cc. of water and then the sodium ethylate and thiourea were added. Some solid separated after warming, 10 cc. more water were added and the solution heated for a half hour longer. On evaporating to dryness, dissolving in 60 cc. of water and precipitating, 3.8 grams of 2-thiothymine were obtained. On recrystallizing from 175 cc. of water 3.2 grams separated.

XIII. Fifty grams of ethyl propionate, 43.5 grams of ethyl formate and 11.3 grams of sodium gave 47.5 grams of dry ethyl sodiumformylpropionate. The ether filtrate was evaporated to dryness and the residue was combined with the above. Calculating on the basis of 65 grams of sodium salt in the entire lot, twenty grams of thiourea (over half molecule) in 500 cc. of 95 per cent. alcohol were added. The mixture was heated three and a half hours, the alcohol was then evaporated and the residue dissolved in 175 cc. of water. When precipitated as in the previous cases, 15 grams of 2-thiothymine were obtained.

XIV. The ether filtrate from a condensation in which 150 grams of ethyl propionate were converted into sodium salt

was evaporated to dryness and treated with 4 grams of sodium in 400 cc. of absolute alcohol and 20 grams of thiourea. The mixture was heated one hour on the steam bath and then evaporated to dryness. Two hundred and fifty cc. of water were added and the solution, on precipitating with acetic acid, gave 9.6 grams of 2-thiothymine. From the average yield of four condensations with the filtered salt it is calculated that the ether solution in this case contained 32.3 grams of ethyl sodiumformylpropionate.

XV. The ether filtrate from the preparation of ethyl sodiumformylpropionate in which 50 grams of ethyl propionate were used was treated as above with 3 grams of sodium in 100 cc. of absolute alcohol and 5 grams of thiourea. The mixture was warmed for 3 hours, then 35 cc. of water were added and the solution was warmed for a half hour longer. On evaporating to dryness, taking up in 50 cc. of water, and adding acetic acid 4.3 grams of 2-thiothymine were obtained.

The following table gives the results of the condensation of ethyl sodiumformylpropionate with thiourea in alcoholic solutions:

	Weight of ethyl so- diumformyl- propionate.	Number of cc. of alcohol for 1 gram of sodium salt.	Weight of 2-thio- thymine obtained.	Calculated weight of 2-thio- thymine from 100 grams ester.	Per cent. yield of 2-thio- thymine.	Calculated weight of thymine from 100 grams ester.
VI	19.0	18.4	6.8	42.3	30.4	37.6
VII	28.0	14.3	8.0	33.8	24.2	30.0
VIII	14.1	18.4	3.4	28.6	20.5	25.3
IX	15.0	10.0	4.0	32.0	23.0	28.4
X	27.0	13.0	8.0	35.0	25.1	31.0
XI	13.2	11.3	3.3	30.0	21.6	26.6
XII	15.0	5.7	3.8	30.4	21.8	27.0
XIII	60.0?	8.3	15.0	30.0	20.1	24.8

Experiments VI, VII, VIII and IX were carried out in absolute alcohol, X, XI and XIII in 95 per cent. alcohol, and XII in 85 per cent. alcohol. Experiment VIII is a duplicate of VI. Sodium ethylate and the calculated quantity of thiourea were present. Number VII was similar except that no sodium ethylate was used. In IX sodium ethylate was present but only one-half the calculated quantity of thiourea

was added. In the remaining experiments sodium ethylate and about one-half the calculated quantity of thiourea was employed, except in X, where one molecular proportion of thiourea was used.

If we exclude experiment VI, which for some unknown reason gave a much higher yield of 2-thiothymine than the others, and also experiment XIII, in which the amount of salt taken was determined by calculation, we find that the average yield of thymine by this method is 28.0 grams from 100 grams of ethyl propionate. This is 22.6 per cent. of the calculated.

Preparation of 2-Thiothymine in Aqueous Solution.—XVI. Seventeen grams of ethyl sodiumformylpropionate were dissolved in a solution of 8.5 grams (one molecule) of thiourea in 65 cc. of water. The solution was allowed to stand for 10 hours, then precipitated with acetic acid. The yield of 2-thiothymine was 2.5 grams.

XVII. (By WALTER F. STOREY.) One hundred grams of propionic ester were condensed with an excess of ethyl formate and a little over (2 grams) one atomic proportion of sodium. When all the sodium had disappeared the calculated quantity (one molecule) of thiourea was added in ice water and the mixture thoroughly shaken. After standing overnight the ether was removed and, after warming, concentrating and cooling, acetic acid was added. The yield was 14.5 grams of the thiopyrimidine.

XVIII. One hundred and fifty grams of ethyl propionate, 115 grams of ethyl formate and 36 grams instead of 33.8 of sodium were used in this experiment. When the sodium had disappeared a solution of 55 grams of thiourea in 400 cc. of water was prepared (38 grams is one-half the calculated amount). Lumps of ice were added to the solution of the salt and the ether solution. The whole was shaken and allowed to stand overnight. The deep red solution was concentrated on the steam bath and finally cooled and acetic acid added. The precipitate weighed 27 grams, and from the filtrate 3 grams more were obtained on standing.

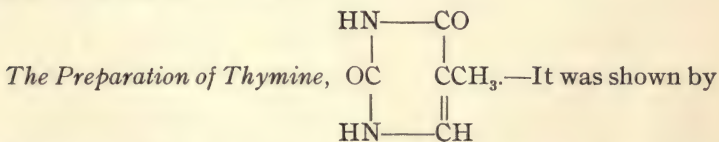
XIX. One hundred grams of each ester were condensed with 2 grams more than the calculated amount of sodium.

The whole was mixed with a saturated solution of 70 grams of thiourea in ice water. After standing a few minutes it was warmed and acetic acid added. Fifteen grams of 2-thiothymine were obtained.

The following table gives the results of the condensation of ethyl sodiumformylpropionate with thiourea in aqueous solution.

	Weight of propionic ester.	Weight of ethyl sodium-formyl-propionate.	Weight of 2-thio-thymine obtained.	Calculated weight of 2-thio-thymine from 100 grams ester.	Per cent. yield of 2-thio-thymine.	Calculated weight of thymine from 100 grams ester.
XVI	...	17 ¹	2.5	17.4	12.5	15.4
XVII	100	120 ¹	14.5	14.5	10.4	12.8
XVIII	150	180 ¹	30.0	20.0	14.4	17.7
XIX	100	120 ¹	15.0	15.0	10.7	13.3

The average yield of thymine by this method is 14.8 grams from 100 grams of ethyl propionate. This is only 11.9 per cent. of the calculated.



Wheeler and Merriam that 2-methylmercapto-5-methyl-6-oxypyrimidine² gave 99 per cent. of the calculated amount of thymine when boiled with hydrochloric acid. The ethylmercapto derivative gives a similar result.

2-Thiothymine, like 2-thiouracil, is easily desulphurized by simply evaporating its aqueous solution with chloracetic acid.³ For example, 3 grams of 2-thiothymine were dissolved in 250 cc. of boiling water and 3 grams of chloracetic acid were added. The solution was then evaporated to dryness on the steam bath and the residue was washed with 15–20 cc. of alcohol. It was free from sulphur and weighed 2.55 grams or 95.8 per cent. of the calculated. On evaporating the alcoholic washings more was obtained. The washed ma-

¹ Calculated from average yield of salt.

² THIS JOURNAL, 29, 487 (1903).

³ *Ibid.*, 40, 552 (1908).

terial consisted of snow-white crystals or scales and it melted at 340° . This is a higher melting point than that observed for thymine from other sources. Fischer and Roeder¹ give 321° , Wheeler and Merriam² 326° . A nitrogen determination by W. F. Storey gave:

	Calculated for $C_8H_8O_2N_2$.	Found.
N	22.22	22.21

In desulphurizing larger quantities it is unnecessary to dissolve all the material at first and relatively less chloracetic acid may be used.

Properties of 2-Thiothymine.—The properties of 2-thiothymine and its salts have been investigated by W. F. Storey. When the substance is first obtained by acidifying the alkaline solutions with acetic acid it separates slowly, usually not all at once, as a crystalline brownish-white precipitate. It has about the same solubility in water as in alcohol and it crystallizes from these solvents in fairly stout prisms, which have a tendency to retain the color of the solutions. One hundred parts of water at 20° dissolved 0.133 part of 2-thiothymine. This is the average of two closely agreeing determinations. Thymine is more than twice as soluble in water. Mr. Storey found that 100 parts of water at 23° dissolved 0.303 part thymine.

	Calculated for $C_8H_8ON_2S$.	Found.
N	19.71	19.67

2-Thiothymine has more pronounced acid properties than thymine. When crystallized from aqueous ammonia it retains ammonia. On drying, the amount of ammonia retained (21.86 per cent. nitrogen) was less than that calculated for a 1 : 1 salt (26.41 per cent. nitrogen). The salts of the alkali metals are very soluble in water. A solution of the sodium salt gave with silver nitrate an amorphous white precipitate, which did not blacken on boiling. The boiling

¹ Ber. d. chem. Ges., **34**, 3751 (1901).

² Loc. cit.

aqueous solution gives a white precipitate with mercuric chloride. It did not blacken on boiling alone or in the presence of alkali.

The sodium salt of 2-thiothymine, $C_5H_5ON_2SNa \cdot 1.5H_2O$, appears to be less soluble than the potassium salt. It was formed by dissolving the pyrimidine in water containing the calculated quantity of sodium hydroxide, concentrating and then crystallizing from aqueous alcohol. It formed radiating prisms which did not melt at 300° .

	Calculated for $C_5H_5ON_2SNa \cdot 1.5H_2O$.	Found.	
N	14.73	14.73	14.58
H ₂ O	14.21	14.65	...

The potassium salt, $C_5H_5ON_2SK \cdot H_2O$, is soluble in less than three parts of water. From dilute alcohol it forms radiating, colorless prisms, similar to the sodium salt.

	Calculated for $C_5H_5ON_2SK \cdot H_2O$.	Found.
N	14.14	13.83

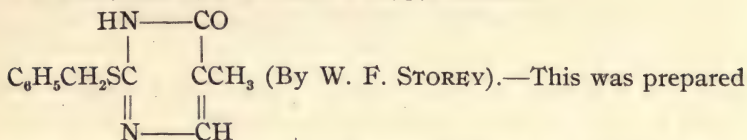
The Copper Salt, $C_5H_4ON_2SCu \cdot H_2O$.—This salt was prepared by adding copper sulphate in aqueous solution to a hot saturated aqueous solution of 2-thiothymine. It formed a green, amorphous precipitate, which was washed with water and dried over sulphuric acid.

	Calculated for $C_5H_4ON_2SCu \cdot H_2O$.	Found.
N	12.58	12.52
H ₂ O	8.08	7.79

It may be mentioned that the corresponding copper salt of 2-thiouracil, which also contains one molecule of water,¹ has a mustard-yellow color. These salts do not blacken on boiling. List² found that 2-thio-4-methyluracil in hot, saturated, aqueous solution gave a yellow precipitate with copper sulphate (this salt was anhydrous), while if the potassium salt was used a green copper salt was obtained.

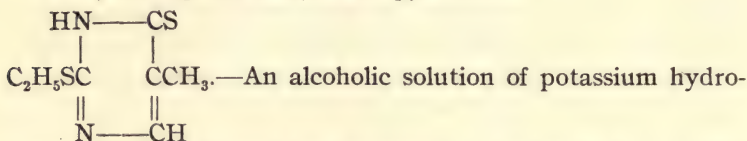
¹ Wheeler and Liddle: *Loc. cit.*

² Ann. Chem. (Liebig), **236**, 9, 11 (1886).

2-Benzylmercapto-5-methyl-6-oxypyrimidine,

from the above potassium salt by warming in alcoholic solution with benzyl chloride. From dilute alcohol it formed colorless needles, which melted to a clear oil at 204° – 205° .

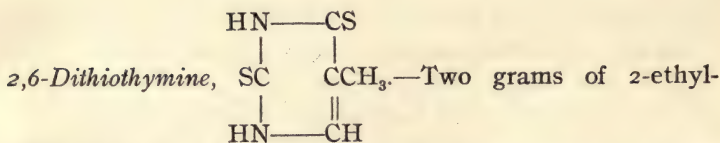
	Calculated for $\text{C}_{12}\text{H}_{13}\text{ON}_2\text{S}$.	Found.
N	12.07	12.25

2-Ethylmercapto-5-methyl-6-thiopyrimidine,

sulphide was prepared by saturating a solution of 57 grams of potassium hydroxide in 250 cc. of alcohol with hydrogen sulphide. To this solution 24 grams of 2-ethylmercapto-5-methyl-6-chlorpyrimidine¹ were added. The reaction began immediately and after warming on the steam bath for nearly an hour the solution was evaporated to dryness. The residue dissolved completely in water and on acidifying with acetic acid a bulky precipitate separated. After washing with water and drying it was found that the yield was practically quantitative. The crude material melted at about 175° to a clear oil and on further heating it solidified at 180° – 190° and remained solid until 280° was reached, when it melted with some effervescence. The substance dissolved easily in boiling alcohol. When the solution was quickly cooled the material crystallized in plates, but when allowed to cool slowly, prismatic needles separated. It then melted at 181° to a clear oil; the pure material, on further heating, did not solidify.

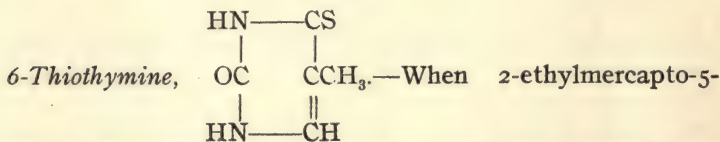
	Calculated for $\text{C}_7\text{H}_{10}\text{N}_2\text{S}_2$.	Found.
N	15.05	14.91

¹ Wheeler and Johnson: *THIS JOURNAL*, **31**, 595 (1904).



mercapto-5-methyl-6-thiopyrimidine were heated in an oil bath at 215° . The substance melted and a small portion sublimed. On passing perfectly dry hydrogen chloride into the molten mass the material almost immediately solidified. The passage of the gas was continued for about five minutes. After cooling, the solid was treated with ammonium hydroxide, which dissolved the greater part, leaving a small amount of a pungent smelling oil. This was separated from the ammonia solution and the latter was acidified with acetic acid. A bulky yellow precipitate resulted, which was only slightly soluble in water but dissolved fairly easily in alcohol, and then, on cooling, gave bunches of small, bright yellow needles. They melted at 281° with decomposition and effervescence.

	Calculated for $\text{C}_6\text{H}_6\text{N}_2\text{S}_2$.	Found.
N	17.94	18.14



methyl-6-thiopyrimidine is heated with strong hydrochloric acid it does not smoothly go into 6-thiothymine as might be expected from analogy with the corresponding 4-methyl compound, but instead it shows a strong tendency to lose sulphur from the 6-position and pass directly into thymine. In fact, by boiling ten grams of the 2-ethylmercapto-6-thiopyrimidine for one and a half hours with strong hydrochloric acid and then twice evaporating to dryness with additional acid, very pure thymine was obtained which, after one recrystallization, gave no test for sulphur and melted at 340° . A nitrogen determination gave 22.22 per cent. nitrogen. This is the calculated value for thymine.

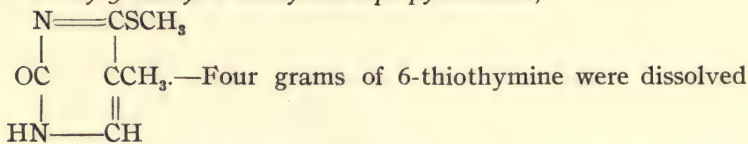
By a less vigorous treatment with acid, the decomposition

was not carried so far and a small yield of 6-thiothymine was obtained. Several experiments were required to show the conditions best adapted to obtaining this result. It was found advisable to stop the hydrolysis while there still remained some unchanged mercapto derivative. This was then extracted by means of alcohol, leaving a mixture of 6-thiothymine with a small amount of thymine. These were separated by crystallizing from water.

Nine grams of 2-ethylmercapto-5-methyl-6-thiopyrimidine were twice evaporated to dryness on the steam bath with 45 cc. of concentrated hydrochloric acid and an equal quantity of water. The dry residue was boiled for a few minutes with 100 cc. of alcohol and the portion which remained undissolved was filtered off. This weighed 4.2 grams. It was dissolved in boiling water and on cooling gave bright yellow, matted, silky needles, which melted with some effervescence at 330° .

	Calculated for $C_6H_6ON_2S$.	Found.
N	19.72	19.98

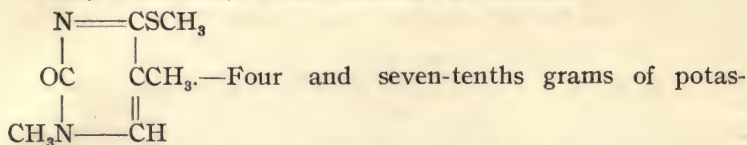
2-Oxy-5-methyl-6-methylmercaptopyrimidine,



with 1.58 grams of potassium hydroxide in 125 cc. of alcohol and 20 cc. of water. The change from the yellow pyrimidine to the potassium salt was marked by an immediate change to a white color. Four grams of methyl iodide were added to the solution and the mixture was warmed for 15 minutes on the water bath and then allowed to stand overnight. The reaction was complete at the end of this time and the solution became neutral. The alcohol was evaporated and the residue was found to be easily soluble in hot water. On crystallizing from this solvent bunches of light yellow, prismatic needles were obtained which, after two recrystallizations from alcohol, melted at 205° – 211° .

	Calculated for $C_6H_8ON_2S$.	I.	Found.	II.
N	17.94	18.08	●	18.14

2-Oxy-3,5-dimethyl-6-methylmercaptopyrimidine,



sium hydroxide and 4.4 grams of 2-oxy-5-methyl-6-methylmercaptopyrimidine were dissolved in 150 cc. of 95 per cent. alcohol. Twelve grams of methyl iodide, or three molecular quantities, were added and the mixture was warmed for an hour on the steam bath under a return condenser. The solution then became neutral. After evaporating off the alcohol, the solid residue was extracted three times with boiling chloroform. An oily residue separated from the chloroform solution which solidified to a white solid on being stirred. It weighed 4.5 grams, or 94 per cent. of the theoretical amount of dimethylmethylmercaptopyrimidine. This material was extremely soluble in alcohol. It also dissolved easily in boiling water and benzene. From benzene solutions it crystallized in clusters of crystals resembling grains of wheat. From the water solutions, which had a marked tendency to remain supersaturated even after standing several hours, the substance crystallized in white, prismatic needles, which melted to a colorless oil at 83°.

	Calculated for $\text{C}_7\text{H}_{10}\text{ON}_2\text{S}$.	Found.
N	16.4	16.6

Treatment with Hydrochloric Acid: 3-Methylthymine.—In order to determine the structure of the above compound two grams of it were boiled for 3 hours with 25 cc. of concentrated hydrochloric acid and an equal quantity of water, under a return condenser. On evaporating off the acid 1.4 grams of a white solid was left behind, which melted at 281°–283°. One crystallization of this from water gave one gram of material melting at 284° and exhibiting all the properties of 3-methylthymine, as described by Johnson and Clapp.¹ Especially noticeable were the two forms of crystals (needles and prisms)

¹ J. Biol. Chem., 6, 49 (1908).

described. When this sample was mixed with a sample of their material the melting point was unchanged.

	Calculated for $C_8H_8O_2N_2$.	Found.
N	20.0	20.1

The mother liquor from this compound was carefully examined for the isomeric 1-methylthymine, but this substance was not found.

In order to determine whether or not any of the isomeric 2-oxy-1,5-dimethyl-6-methylmercaptopyrimidine had been formed with the 3,5-dimethyl derivative, the mother liquors from the crystallization of 2-oxy-3,5-dimethyl-6-methylmercaptopyrimidine were boiled for 3 hours with hydrochloric acid, under a return condenser. After evaporating the acid the solid residue weighed 1.1 grams. From this, by crystallizing from water, were recovered 0.8 gram of nearly pure 3-methylthymine, melting at 275° – 281° and showing the characteristic properties. There was also obtained a very small quantity (0.15 gram) of another substance which sublimed in white needles. This substance melted at 153° – 155° and was extremely soluble in water and alcohol. Not enough was obtained for analysis, but it is probable that it was 1,3-dimethylthymine, described by Johnson and Clapp. They give the melting point as 153° . When our material was mixed with theirs the melting point was not lowered. The formation of 1,3-dimethylthymine may be explained by supposing a small amount of thymine to have been left in the 6-thiothymine. The difficulty of obtaining 6-thiothymine free from thymine has been noted above. Thymine, on methylation, would give 1,3-dimethylthymine.

No evidence could be found here of the presence of 1-methylthymine. It seems fair to conclude, therefore, that under the conditions employed in the methylation of this 6-methylmercaptopyrimidine only a 3-derivative was formed.

VII. ON SOME PICROLONATES: GUANIDINS.

By HENRY L. WHEELER AND GEORGE S. JAMIESON.

(*From the Sheffield Laboratory of Yale University.*)

(Received for publication, December 13, 1907.)

In a paper recently published by one of us¹ on some salts of cytosin, isocytosin, 6-aminopyrimidin and 6-oxypyrimidin the melting or effervescing points of the picrolonates were given. When these salts were first prepared it was found that Kjeldahl's method of analysis gave low results. The method was as follows: About 0.11–0.12 gram of substance was added to 20 cc. of sulphuric acid, then 2 or more grams of zinc dust and finally 15 grams of potassium sulphate; the digestion then being carried on as usual. On the other hand this method proved successful in the case of the corresponding picrates.

The picrolonic acid which we used was obtained from Kahlbaum. It was shown to be a pure sample by an absolute nitrogen determination and by a carbon and hydrogen determination, but the analysis of this material by Kjeldahl's method also gave results that were several per cent less than the calculated.

The difficulty was finally found to be due to the insolubility of picrolonic acid in concentrated sulphuric acid since Kjeldahl's procedure gave results agreeing with the calculated when the reduction was carried out in dilute sulphuric acid with the addition of some alcohol. Although numerous picrolonates have recently been described it appears that nitrogen in these salts has invariably been determined by the absolute method.²

Before correct results had been obtained in the analysis of our sample of picrolonic acid and in order to identify the material

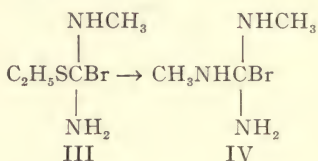
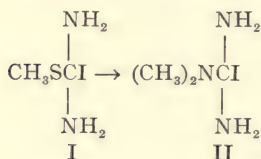
¹ This *Journal*, iii, p. 285, 1907.

² For a list of papers on picrolonates up to the year 1907, see Matthes and Rammstedt: *Archiv d. Pharmazie*, ccxlv, p. 112, 1907. Since then, Levene: *Biochem. Zeitschr.*, iv, p. 320, 1907, and Warren and Weiss: This *Journal*, iii, p. 327, 1907.

the guanidin salt was prepared. This salt agreed in properties with the description of guanidin picrolonate given by Schenck.¹

The action of aqueous solutions of amines, primary or secondary, or ammonia on the alkylhalide addition products of thioureas affords a very convenient method for the preparation of certain substituted guanidins, especially those that have been found in meat extract² and urine.³

The action takes place at ordinary temperature, mercaptan is liberated, and on evaporating, a guanidin salt is obtained. For example, when the methyl iodide addition product of thiourea, I (2-methylpseudothiureahydriodide), was dissolved in an excess of a 33 per cent solution of dimethylamine bubbles of methylmercaptan escaped. After evaporating off the excess of amine by warming, then adding a hot aqueous solution of picrolonic acid, unsymmetrical dimethyl guanidin (2, 2-dimethyl guanidin) picrolonate separated. This salt agreed with the description of dimethyl guanidin picrolonate given by Kutscher.⁴



The hydrobromide of the isomeric symmetrical dimethyl guanidin, IV (1, 2-dimethyl guanidin), was obtained by treating the ethylbromide addition product of methylthiourea, III, (1-methyl-2-ethylpseudothiurea) with methylamine.

The melting point of the picrolonate prepared from this substance was identical with that assigned to symmetrical dimethyl guanidin picrolonate by Schenck.⁵

Monomethyl guanidin hydrobromide was prepared in two ways, by dissolving the ethylbromide addition product of thiourea in an aqueous solution of methylamine and by dissolving the corresponding addition product of methylthiourea in concentrated

¹ *Zeitschr. f. physiol. Chem.*, xlv, p. 427, 1905.

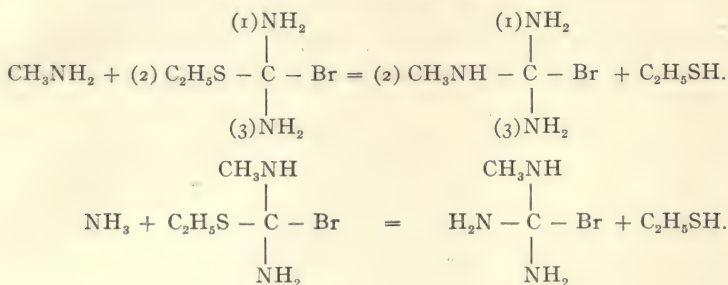
² Kutscher and Lohmann: *Zeitschr. f. physiol. Chem.*, xlviii, p. 1, 1906.

³ Achelis: *Ibid.*, 1, p. 10, 1906; Kutscher: *Ibid.*, li, p. 457, 1907.

⁴ *Loc. cit.*

⁵ *Zeitschr. f. physiol. Chem.*, xlviii, p. 423, 1906.

ammonia. As would be expected from the non-existence of tautomeric forms in the case of the amidines¹ the picrolonates of the material prepared by these two methods were identical. The reactions and the substances may be represented as follows:



The nomenclature hitherto employed for pseudothiureas and guanidins (symmetrical and unsymmetrical) is not sufficient to define substituted derivatives in general. The writer therefore proposes to use that system which has been found so convenient in the purin² and pyrimidin series, namely, of assigning numbers (as shown above) to indicate the position of substituents in the case of the pseudourea, pseudothiurea and guanidin derivatives. Dieckmann³ has used this system for parabanic acid compounds.

This then brings about a systematic nomenclature for all these related substances.

EXPERIMENTAL PART.

Cytosin Picrolonate, $\text{C}_4\text{H}_5\text{ON}_3 \cdot \text{C}_{10}\text{H}_8\text{O}_5\text{N}_4$.—A half a gram of cytosin in a 100 cc. of water was added to one gram of picrolonic acid in about 350 cc. of hot water. On rapidly cooling the solution an amorphous, gelatinous precipitate separated. On slowly cooling or on crystallizing from water little balls of fine bright yellow needles or slender prisms separated. This salt is very difficultly soluble in alcohol from which it is obtained in flat prisms or plates. It melts with effervescence about 270° – 273° .

The nitrogen determinations in the case of this and the other picrolonates were determined by Kjeldahl's method as follows:

¹ Wheeler and Johnson: *Amer. Chem. Journ.*, xxxi, p. 577, 1904.

² *Ber. d. deutsch. chem. Gesellsch.*, xxx, p. 549, 1897.

³ *Ibid.*, xl, p. 3737, 1907.

About 0.1 gram of substance was dissolved in a mixture of 35 cc. of alcohol and 20 cc. of dilute sulphuric acid. Two grams of zinc dust were used for the reduction and the solution was warmed until colorless. Then 10 cc. of concentrated sulphuric acid and 12 grams of potassium sulphate were added, the water and alcohol was evaporated and the residue was digested for two or three hours. The analysis was then finished in the usual manner.

	Calculated for $C_{14}H_{13}O_6N_7$:	Found:
N	26.13	26.15

Since this salt was prepared by us it has been obtained by Levene.¹ He gives the formula $C_4H_6N_3 \cdot C_{10}H_8N_4O_5$, which is evidently a typographical error.

2-Amino-6-oxypyrimidin (Isocytosin) Picrolonate, $C_4H_5ON_3 \cdot C_{10}H_8O_5N_4$.—A half a gram of isocytosin and 1.2 gram of picrolonic acid, on mixing the hot aqueous solutions (about 400 cc.), gave an immediate, bulky precipitate consisting of very fine, yellow hair-like needles. This salt is practically insoluble in alcohol and its melting or effervescing point varies with the rate of heating. It usually decomposes about 273° - 275° .

	Calculated for $C_{14}H_{13}O_6N_7$:	Found:
N	26.13	26.05

6-Aminopyrimidin Picrolonate, $C_4H_5N_3 \cdot C_{10}H_8O_5N_4$.—A solution of 0.1 gram of 6-aminopyrimidin in 4 cc. of water was added to 0.3 gram picrolonic acid in 100 cc. of hot water. This gave an immediate precipitate and on cooling, the salt separated in the form of interlaced, yellow, hairlike needles. The yield was 0.35 gram, calculated, 0.4 gram. It melted with effervescence at 261° ; on rapidly heating it melted a few degrees higher.

	Calculated for $C_{14}H_{13}O_5N_7$:	Found:
N	27.29	27.10

6-Oxypyrimidin Picrolonate, $C_4H_4ON_2 \cdot C_{10}H_8O_5N_4$.—A solution of 0.2 gram of 6-oxypyrimidin in 6 cc. of water was added to a hot solution of 0.55 gram picrolonic acid in 125 cc. of water.

¹ *Biochem. Zeitschr.*, iv, p. 320, 1907.

This gave an immediate precipitate and on cooling, a bulky mass of slender, yellow needles separated. The yield was 0.55 gram. When this was heated it showed signs of change at 180° and then melted with vigorous effervescence at 222° . The salt was recrystallized from water and from alcohol. It then melted suddenly, in both cases, at 191° – 193° . It is difficultly soluble in alcohol and it separates from this solvent in thin scales or plates.

	Calculated for $C_{14}H_{12}O_6N_6$	Found:
N	23.33	23.33

Methylguanidin Picrolonate, $C_2H_7N_3 \cdot C_{10}H_8O_5N_4$.—2-Ethyl-pseudothiourea hydrobromide was dissolved in an excess of a 33 per cent solution of methylamine and allowed to stand over night. The excess of amine and mercaptan was then evaporated and the solution, after filtering from a slight turbidity, was divided into two parts. One part was precipitated with picric acid; the picrate formed needles which melted sharply at 200° . Fischer¹ gives the melting point of methyl guanidin picrate at 200° .

The remaining solution was precipitated with an aqueous solution of picrolonic acid. The salt formed a compact, not bulky, yellow precipitate which when recrystallized from water formed minute, diamond shaped tables or blocks. It decomposed with effervescence at 291° .

	Calculated for $C_{12}H_{15}O_5N_7$	Found:
N	28.24	28.23

1-Methylguanidin was also prepared by dissolving 1.5 gram of 1-methyl-2-ethylpseudothiourea hydrobromide in concentrated ammonia. On evaporating the solution and adding an aqueous solution of picrolonic acid the precipitate obtained was identical with the above.

2,2-Dimethylguanidin Picrate, $C_3H_9N_3 \cdot C_6H_3O_7N_3$.—The guanidin was prepared by dissolving 2-ethylpseudothiourea hydrobromide in a strong, aqueous solution of dimethylamine. The precipitate produced by adding an aqueous solution of picric acid was crystallized from water. It formed small, pointed,

¹ Ber. d. deutsch. chem. Gesellsch. xxx, p. 2414, 1897.

yellow prisms or branch-like growths. It melted to an oil without effervescence at 224° .

	Calculated for $C_9H_{12}O_7N_6$:	Found:
N	26.58	26.53

2,2-Dimethylguanidin Picrolonate, $C_3H_9N_3 \cdot C_{10}H_8O_5N_4$.—The guanidin was prepared as above and also by the action of dimethylamine on 2-methylpseudothiurea hydriodide. The solutions gave an immediate precipitate with aqueous picronic acid. The salt was crystallized from water, it then formed small, flat, four-sided, yellow prisms which decomposed with effervescence quite sharply at 278° . Kutscher and Lohmann give the melting point of their dimethylguanidin picrolonate obtained from urine at 275° – 278° .¹

This salt is very difficultly soluble in alcohol from which it forms needle-like prisms.

	Calculated for $C_{13}H_{17}O_5N_7$:	Found:
N	27.13	27.13

1,2-Dimethylguanidin Picrate, $C_3H_9N_3 \cdot C_6H_3O_7N_3$.—One gram of 1-methyl-2-ethylpseudothiurea hydrobromide was treated with an excess of strong aqueous methylamine solution. The picrate formed yellow prisms with uneven striated faces. It melted to a clear oil at 178° .

	Calculated*for $C_9H_{12}O_7N_6$:	Found:
N	26.58	26.58

A portion of the guanidin solution was precipitated with picronic acid. This precipitate crystallized from water in thin, yellow plates which melted at 262° . It agreed with the description given by Schenck² who gives the melting point 260° – 262° . This also confirms the conclusion of Kutscher and Lohmann that the dimethyl guanidin from urine has the isomeric structure.

In preparing guanidins by the above method an excess of amine must be used and the solutions should be strong, in order to bring about a complete reaction. Otherwise unaltered pseudothiurea will be precipitated as picrate or picrolonate.

¹ *Zeitschr. f. physiol. Chem.*, xlviii, p. 423, 1906.

² *Ibid.*

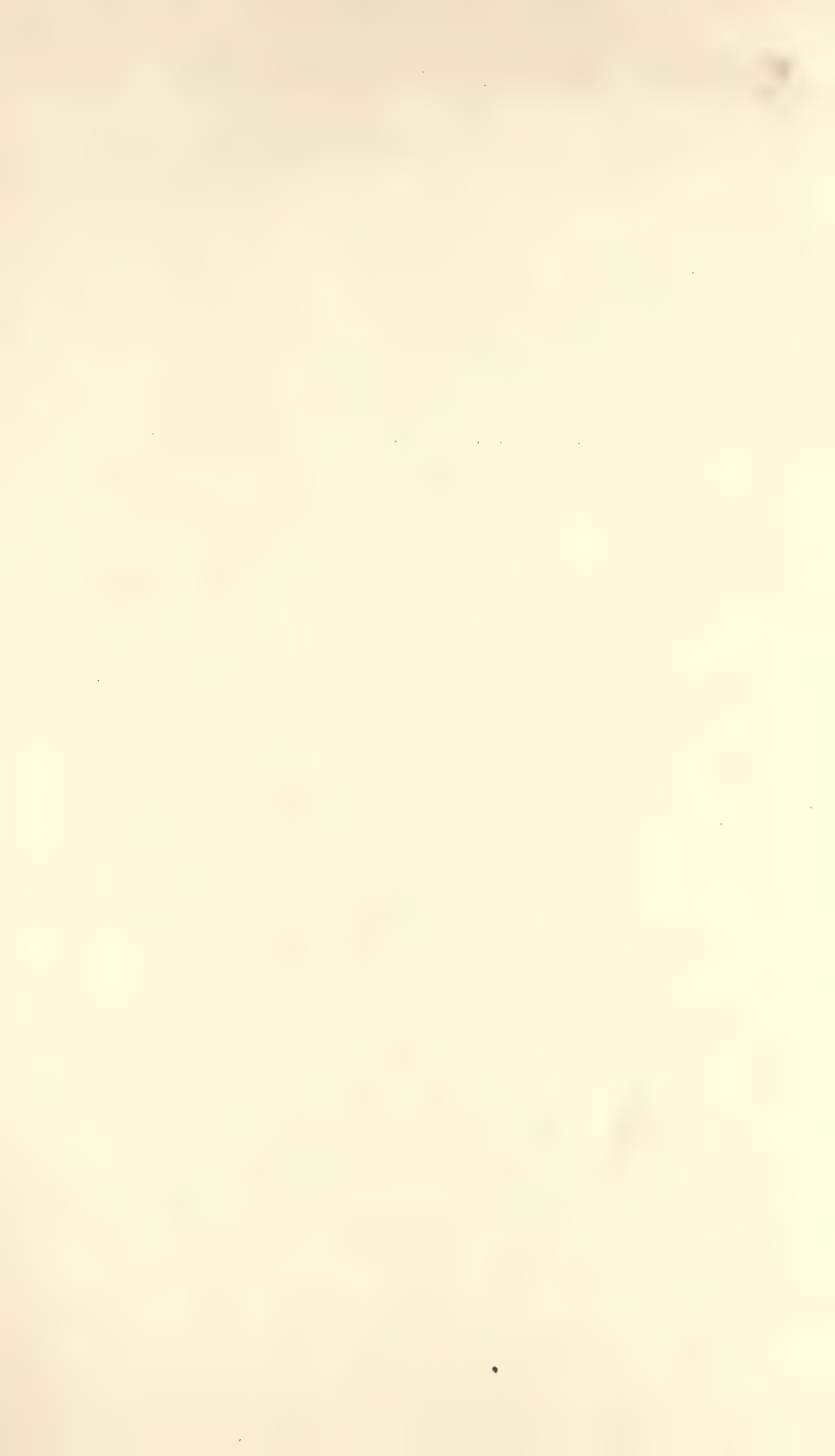
2-Ethylpseudothiourea Picrate, $C_3H_8N_2S.C_6H_3O_7N_3$, separates from aqueous solutions in flat, yellow prisms which melt at 184° to a clear oil.

	Calculated for $C_9H_{11}O_7N_5S$:	Found:
N	21.02	21.00

2-Ethylpseudothiourea Picrolonate, $C_3H_8N_2S.C_{10}H_8O_5N_4$, forms difficultly soluble, flat, yellow prisms which melt at 225° .

	Calculated for $C_{13}H_{16}O_5N_6S$:	Found:
N	22.82	22.69

1-Methyl-2-ethylpseudothiourea forms a picrate which crystallizes in yellow prisms and melts to a clear oil at 157° .



BIBLIOGRAPHY

1817.

Brugnatelli, Erythriscbe Säure. *Ann. chim, phys.*, 8. 201.
Schweigg. *Jour.* 24, 208. *Phil. Mag.* 52, 30. (Alloxan from Uric Acid.)

1818.

Prout. Uramil. (als Zersetzungsproduct des purpursäuren Ammonium). *Phil. Trans.* 1818, 420.

1820.

Prout. Oxydation of Murexid to Alloxan. *Annals of Philosophy*, (London) 14, 363.

1838.

J. Fritzsche, Ueber Uroxin, (Alloxan). *Bull. scientif. de Petersb.* No. 78. *Centr. B.* 1838, 401.

F. Wöhler und J. Liebig, Untersuchungen über die Natur der Harnsäure. (Erste Abtheilung). *Ann.* 26, 241. *Centr. B.* 1838, 639.

1839.

J. Fritzsche, Vorläufige Notiz die Purpursäure und ihre Salze. *Ann.* 29, 331; 32, 316. *J. prakt. Chem.* 16, 380; 17, 42.

Gmelin. Murexid. *Handb. organ. Chem.* 2, 320.

1844.

W. Gregory, Ueber die Zersetzungsproducte der Harnsäure. *Philos. Mag.* 186, 1844. *Centr. B.* 1844, 246.

1845.

A. Schlieper, Ueber Alloxan, Alloxansäure und einige neue Zersetzungsproducte der Harnsäure. *Ann.* 55, 263; 56, 1. *Centr. B.* 1846, 5.

1846.

W. Gregory, Ueber die Bereitung des Alloxans. *Philos. Mag.* (3) 28, 550. *Centr. B.* 1846, 510.

1848.

F. Wöhler und F. Frerichs, Ueber die Veränderungen, welche namentlich organische Stoffe bei ihrem Uebergang in den Harn erleiden. *Ann.* 65, 335. *Centr. B.* 1848, 353.

E. Frankland und H. Kolbe, Ueber die Zersetzungsproducte des Cyanäthyls durch Einwirkung von Kali. (Kyanäthin). *Ann.* 65, 269. *Centr. B.* 1848, 369.

1849.

F. Röchleder, Notiz über das Caffein. Ann. 69, 120. Centr. B. 1849, 262.

Ibid. Notiz über das Caffein. Ann. 71, 1. Wien. Acad. Ber. 1849, 93. Pharm. Centr. 1849, 262, 849. Centr. B. 1849, 849.

1850.

F. Rochleder, Ueber die Zersetzungsproducte des Caffeins. Ann. 71, 56. Centr. B. 1850, 58.

F. Rochleder, Notiz über das Cholestrophan. Ann. 73, 123. Centr. B. 1850, 182.

1851.

F. Rochleder, Weiteres über das Caffein. Sitzungsber. d. kaiserl. Akad. der Wiss. Wien 1850, 1. Bentr. B. 1851, 41.

G. Stäedeler, Ueber die Uroxansäure, ein Zersetzungsproducte der Harnsäure. Centr. B. 1851, 604.

G. Stäedeler, Berichtigung in Betreff der Uroxansäure. Ann. 80, 119. Centr. B. 1851, 902.

1854.

W. Gregory, Freiwillige Umsetzung des Alloxans. Ann. 87, 126. Centr. B. 1854, 176.

Sacc, Anwendung des Murexids in der Färberei. Pharm. Jour. 14, 30. Centr. B. 1854, 896.

1856.

G. Stäedeler, Ueber die Alloxansäure. Ann. 97, 120. Centr. B. 1856, 161.

H. Hlasiwetz, Ueber einige Salze des Harnstoffes mit organischen Säuren. Sitzungsber. d. Akad. d. Wiss. Wien 1856. Centr. B. 1856, 481.

1858.

A. Rosing and L. Chichkoff, Sur l'action du cyanhydrate d'ammoniaque sur l'alloxane. Compt. rend. 1858, 104. Centr. B. 1858, 344.

F. Beilstein, Ueber das Murexid. Ann. 107, 176. Centr. B. 1858, 769.

C. Weltzien, Ueber die Darstellung der Cyansäure und des Amelids aus dem Harnstoff. Ann. 107, 219. Centr. B. 1858, 828.

F. C. Calvert, Ueber die Darstellung von Farbstoffen mittels der im Steinkohlen theer enthaltenen Alkaloide und über das Färben und Drucken der Zenge mit Murexid. Polytechn. Jour. 149, 137. Centr. B. 1858, 909.

G. Lang und Grailich. Krystalle des Alloxans (Messungen). Wien. Akad. Ber. 27, 180.

Wuth, Verbindungen des Alloxans mit säuren schweflig-säuren Alkalien. Ann. 108, 41. J. pr. Chem. 75, 481. Centr. B. 1859, 108.

1859

G. Jac. Brann, Ueber die Darstellung des Murexids im Grossen. Ding. poly. Jour. 152, 193. Centr. B. 1859, 389.

1860.

A. Strecker, Ueber die Zersetzung des Alloxans durch Einwirkung der Cyanüre. Ann. 113, 47. Centr. B. 1860, 289.

W. Heintz, Freiwillige Zersetzung des Alloxans. Pogg. Ann. 111, 436. Centr. B. 1861, 81.

G. Rath, Krystallographische Beiträge. Pogg. Ann. 110, 93.

1861.

W. Heintz, Freiwillige Zersetzung des Alloxans. Pogg. Ann. 110, 93.

1862.

A. Strecker, Ueber die Zersetzung des Caffeins durch Barythydrat. Ann. 123, 360.

Ibid. Notiz über eine eigenthumliche Oxydation durch Alloxan. Ann. 123, 363.

1863.

A. Baeyer, Untersuchungen über die Harnsäuregruppe (Erste Abhandlung.) Ann. 127, 199. Centr. B. 1864, 97.

1864.

L. Hardy, Decomposition de l'acide urique par le brome et action de la chaleur sur l'alloxane. Compt. rend. 1864, 911. Centr. B. 1864, 921.

C. Finck, Zersetzungsproducte des thionursäuren Ammoniaks. Ann. 132, 298.

A. Baeyer, Untersuchungen über die Harnsäuregruppe (Zweite Abhandlung.) Ann. 130, 129. Centr. B. 1864, 929.

1865.

E. Dietrich, Reaction auf Harnsäure. Zeit. f. anal. Chem. 4, 176. Centr. B. 1866, 286.

1866.

C. Heintzel, Ueber die Malonsäure. Ann. 139, 129. Centr. B. 1866, 828.

1867.

G. Lang, Alloxan im Harn eines Herzkranken. Zeit. anal. Chem. 6, 294. Centr. B. f. med. Wiss. 1867, 83.

1868.

A. Strecker, Bildung von Glycocoll aus Harnsäure. Ann. 146, 142. Compt. rend. 66, 538. Zeit. f. Chem. 4, 215. Centr. B. 1868, 334.

O. Schultzen und W. Filehne, Ueber die Einwirkung der Schwefelsäure auf Harnsäure. Ber. 1, 50. Centr. B. 1868, 499.

J. von Liebig, Darstellung des Alloxans. Ann. 147, 366. Centr. B. 1868, 622.

1869.

A. G. Bayer, Ueber eine dem Kyanäthin homologe Basis. Ber. 2, 319.

1870.

N. Menschutkin, Zur Kenntniss der Harnstoffverbindungen, Die Ureide (Erste Abhandlung). Ann. 153, 83. Centr. B. 1870, 219.

H. Kolbe, Ueber die chemische Constitution der Harnsäure und ihrer Derivate. Ber. 3, 183. J. prakt. Chem. 1, 134. Centr. B. 1870, 296.

A. Strecker, Ueber Uroxansäure und die chemische Constitution der Harnsäure. Ann. 155, 177. Centr. B. 1870, 578.

1871.

M. Nencki, Untersuchungen über die Harnsäuregruppe: Alloxan Sulphopseudoharnsäure (Erste Mittheilung). Ber. 4, 722. Centr. B. 1871, 692.

1872.

M. Nencki, Untersuchungen über die Harnsäuregruppe (Zweite Mittheilung). Ber. 5, 45. Centr. B. 1872, 229. (Dritte Mittheilung) Ber. 5, 886. Centr. B. 1872, 802.

1873.

E. Mulder, Ueber von Harnsäure abgeleitete Körper. Ber. 6, 1010. Centr. B. 1873, 675.

F. Wurtz, Action de l'iode sur l'acide urique. Compt. rend. 77, 1548. Centr. B. 1874, 121.

1874.

F. Salomon, Einige Bemerkungen über den Zusammenhang der Allophansäure, Oxalursäure und Alloxansäure. J. prakt. Chem. 9, 290. Centr. B. 1874, 449.

M. L. Magnier de la Source, Action du brome sur l'acide urique. Contribution a l'etude des isalloxanates et de la murexide. Bull. soc. chim. 22, 56. Centr. B. 1874, 581.

1875.

L. Medicus, Zur Constitution der Harnsäuregruppe. Ann. 175, 230.

E. Grimaux, Recherches sur le groupe urique. Compt. rend. 80, 828. Centr. B. 1875, 372.

J. Reoch, Notes on Alloxantin and Murexide. Chem. News 30, 179.

J. Reoch, Constitution of Murexide. Chem. News 30, 265. Centr. B. 1875, 117.

E. Mulder, Ueber Uroxansäure und Allantoxansäure. Ber. 8, 1291.

1876.

N. Menshutkin, Tartronaminsäure. Ber. 9, 1030. Centr. B. 1876, 627.

J. Murdoch und O. Doëbner, Ueber Hydurilsäure. Ber. 9, 1102. Centr. B. 1876, 644.

L. Medicus, Spaltung der Uroxansäure. Ber. 9, 1162. Centr. B. 1876, 709.

N. Menshutkin, Ueber die Zusammensetzung der dialursäuren Salze. Ann. 182, 70. Centr. B. 1876, 708. Tartronaminsäure. Ann. 182, 82. Centr. B. 1876, 708.

1877.

E. Grimaux, Recherches synthetiques sur la serie urique. Ann. chim. phys. (5) 11, 356. Centr. B. 1877, 612.

1878.

E. Mulder, Synthese des cyanacetylurées et de la murexone. Bull. soc. chim. 29, 531. Centr. B. 1878, 612.

E. Grimaux, Synthese des derives uriques de la serie de l'alloxane. Compt. rend. 87, 752. Centr. B. 1879, 4.

1879.

E. Grimaux, Synthese des derives uriques de la serie de l'alloxane. Compt. rend. 88, 85. Bull. soc. chim. 31, 146. Ber. 11, 378. Centr. B. 1879, 212.

E. Grimaux, Sur l'acide pseudo-urique. Bull. soc. chim. 31, 535.

E. Mulder, Ureide, Synthese von Dimethylbarbitursäure. Ber. 12, 465. Centr. B. 1879, 340.

1880.

C. F. Mabery und H. B. Hill, Ueber die Oxydationsprodukte der Dimethylharnsäure. Ber. 13, 739. Centr. B. 1880, 342.

1881.

E. Mulder, Einwirkung von Brom auf Uramil. Ber. 14, 1060. Centr. B. 1881, 424.

M. Conrad und M. Guthzeit, Ueber Barbitursäure. Ber. 14, 1643. Centr. B. 1881, 627.

1882.

M. Nencki und N. Sieber, Ueber zwei neue Derivate des Sulfoharnstoffs. Jour. p. Chem. 25, 72. Centr. 8. 1882, 219.

R. Maly und R. Andreasch, Studien über Caffein und Theobromin. Monats. 3, 92. Centr. B. 1882, 393.

R. Andreasch, Ueber gemischte Alloxantine. Monats. 3, 428. Centr. B. 1882, 634.

R. Andreasch, Ueber Cyamidamalinsäure. Monats. 3, 433. Centr. B. 1882, 635.

M. Conrad und M. Guthzeit, Ueber Barbitursäure. Ber. 15, 2844. Centr. B. 1883, 178.

1883.

R. Behrend, Ueber die Einwirkung von Harnstoff auf Acetessigäther (Vorläufige Mittheilung). Ber. 16, 3027.

E. Fischer und L. Reese, Caffein, Xanthin und Guanin. Ann. 221, 336.

E. von Meyer, Zur Kenntniss des Kyanmethins. J. prakt. Chem. 27, 152. Centr. B. 1883, 343.

1884.

E. Schilling, Ueber Caffeinmethylhydroxid. Zeit. Naturwissensch. (4) 3, 207. Centr. B. 1884, 811.

A. Pinner, Ueber die Einwirkung von Acetessigäther auf die Amidine (Vorläufige Mittheilung). Ber. 17, 2519.

R. Behrend, Ueber einige des Harnstoffs. Ber. 17, 2846.

1885.

R. Behrend, Versuche zur Synthese von Körpern der Harnsäurereihe. Ann. 229, 1. Centr. B. 1885, 679.

G. Ciamician und P. Magnaghi, Ueber die Einwirkung von Phosphorpentachlorid auf Alloxan. Ber. 18, 3444.

Ibid. Versuche zur Synthese von Körpern der Harnsäurereihe. Ann. 231, 248. Centr. B. 1886, 123.

A. Pinner, Ueber die Einwirkung von Acetessigäther auf die Amidine. *Pyrimidine*. Ber. 18, 759; 18, 2845.

1886.

R. Behrend, Ueber das Verhalten von substituirtten Harnstoffen gegen Acetessigäther. Ann. 233, 1. Centr. B. 1886, 453.

1887.

R. List, Zur Constitution von Thioharnstoff und Acetessigäther. Ann. 236, 1. Centr. B. 1887, 1, 83.

A. Köhler, Ueber Nitroderivate des Methyluracils. Ann. 236, 32. Centr. B. 1887, I, 58.

R. Behrend, Ueber eine neue Bildungsweise der Dibrom- und Dichlorbarbitursäure. Ann. 236, 57. Centr. B. 1887, I, 85.

N. Kowalewsky, Einwirkung des Alloxantins auf das Blut. Med. Centr. B. 25, 658. Centr. B. 1887, II, 1296.

R. Behrend, Versuche zur Synthese von Körpern der Harnsäurereihe. Ann. 240, 1. Centr. B. 1887, II, 1311.

G. Pellizzari, Verbindungen des Alloxans mit den aromatischen Aminen. L. Orosi. 10, 295. Centr. B. 1887, II, 1396.

M. Wernecke, Beiträge zur Kenntniss des Caffeins und Caffeidins. (Inaug. Dissertat. Marburg). 1887, 1. Centr. B. 1887, II, 1084.

G. Pellizzari, Oxydierende Wirkung des Alloxans auf einige Organische Substanzen. L. Orosi. 10, 217. Centr. B. 1887, II, 1162.

Ibid. Verbindungen des Alloxans mit den aromatischen Aminen. L. Orosi. 10, 253. Centr. B. 1887, II, 1288.

A. Pinner, Ueber Pyrimidine. Ber. 20, 2361. Centr. B. 1887, 1289.

A. Michael, Preliminary Notes (Malonylguanidine). Amer. Chem. Jour. 9, 219.

1888.

M. Hagen, Ueber dimethylirtes Methyluracil. Ann. 244, 1. Centr. B. 1888, I, 517.

R. Behrend und O. Roosen, Ueber synthetische Versuche in der Harnsäurereihe (Vorläufige Mittheilung). Ber. 21, 999. Centr. B. 1888, I, 546.

R. Behrend, Ueber ein Diazoderivat des Methyluracils. Ann. 245, 213. Centr. B. 1888, I, 832.

G. Glock, Ueber p-Tolenylimidoäther. Ber. 21, 2650. Centr. B. 1888, II, 1333.

Ibid. Ueber Phenylen-*p*-diacetimidoäther. Ber. 21, 2659. Centr. B. 1888, II, 1334.

G. Pellizzari, Alloxandisulfite organischer Basen. L. Orosi. 11, 253. Centr. B. 1888, II, 1546.

Ibid. Verbindungen des Alloxans mit den Pyrazolbasen. Gaz. 18, 340. Centr. B. 1889, I, 16.

Ibid. Alloxandisulfite organisches Basen. Gas. 18, 329. Centr. B. 1889, 1, 19.

1889.

E. von Meyer, Chemische Constitution des Kyanäthins und ähnlicher Verbindungen. J. prakt. Chem. 39, 156. Centr. B. 1889, I, 373.

R. Holtzwardt, Beiträge zur Kenntniss der Polymerisation von Nitrilen Ueber dimolekulares Cyanmethyl. J. prakt. Chem. 39, 230. Centr. B. 1889, I, 623.

R. Wache, Ueber die Polymerisation einiger Nitrile. J. prakt. Chem. 39, 245. Centr. B. 1889, I, 624.

E. von Meyer, Chemische Constitution des Kyanäthins nebst Beiträgen zur Kenntniss derselben und seiner Abkömmlinge. J. prakt. Chem. 39, 262. Centr. B. 1889, I, 625.

G. Pellizzari, Alloxan und Pyrazolbasen. *Ann. di Chim. e. di Farmacologia*, 9, 273. *Centr. B.* 1889, II, 329.

R. Behrend, J. Hoffmann und M. Lehmann, Ueber Alkyl-derivate des Methyluracils und des Nitrouracils. *Ann.* 253, 65. *Centr. B.* 1889, II, 648.

A. Pinner, Ueber Amidine und Pyrimidine. *Ber.* 22, 1600. *Centr. B.* 1889, II, 655.

Ibid. Ueber Pyrimidine. *Ber.* 22, 1612. *Centr. B.* 1889, II, 655.

E. von Meyer, Notiz über Oxymiazine (Oxypyrimidine). *J. prakt. Chem.* 40, 303. *Centr. B.* 1889, II, 876.

A. Pinner, Ueber Pyrimidine. *Ber.* 22, 2609. *Centr. B.* 1889, II, 975.

1890.

A. Pinner, Ueber die Einwirkung von Benzamidin auf Acetylmalonsäureäther. *Ber.* 23, 161. *Centr. B.* 1890, I, 476.

Fausto und Leone Sestini, Ueber die ammoniakalische Gärung der Harnsäure. *Gaz.* 20, 133. *Centr. B.* 1890, I, 1064.

S. Hoogewerf et W. A. Van Dorp, Sur l'action de l'hypobromite de potassium sur la succinphenylamide. *Rec. d. Trav. Chim.* 9, 33. *Centr. B.* 1890, II, 143.

R. Schwaize, Beiträge zur Kenntniss der Polymerisation von Nitrilen. *J. prakt. Chem.* (2) 42, 1. *Centr. B.* 1890, II, 336.

R. Behrend und P. Ernert, Ueber Diazouracilcarbonsäure und deren Derivate. *Ann.* 258, 347. *Centr. B.* 1890, II, 507.

Ibid. Ueber die Condensation von Harnstoff und Acetessigäther. *Ann.* 258, 360. *Centr. B.* 1890, II, 509.

A. Pinner, Ueber die Einwirkung von Benzamidin auf aromatische Orthooxysäureäther. *Ber.* 23, 2934. *Centr. B.* 1890, II, 693.

Ibid. Ueber Imidoäther. *Ber.* 23, 2942. *Centr. B.* 1890, II, 695.

E. Pinner und F. Eschbaum, Ueber Imidoäther des Milchsäure und des Mandelsäurenitrile. *Ber.* 23, 2947. *Centr. B.* 1890, II, 695.

E. Pinner und P. Eberhardt, Ueber Imidoäther aus Ortho- und Paraoxyäthylbenzonitril. *Centr. B.* 1890, II, 695.

A. Pinner, Ueber die Umwandlung der Nitrile in Imidoäther. *Ber.* 23, 2917. *Centr. B.* 1890, II, 696.

A. Pinner und R. Dietz, Ueber Imidoäther des Trimethylen- cyanids. *Centr. B.* 1890, 694.

E. Schmidt und M. Wernecke, Ueber das Caffeidin. *Archiv. Pharm.* 228, 516. *Centr. B.* 1890, II, 817.

T. Curatolo, Methylguanil und Trimethylguanil. *Gaz.* 20, 585. *Centr. B.* 1890, II, 950.

A. Pinner. Notizen über Imidoäther und deren Derivate. Ber. 23, 3820. Centr. B. 1891, I, 318.

1891.

G. Pellizzari, Anilguanidin. Centr. B. 1891, I, 659.

J. Jäeger, Über die Condensation von Guanidin mit *B*-Ketonsäureestern. Ann. 262, 365. Centr. B. 1891, I, 787.

O. Kuhlung, Ueber die Hydrazone des Alloxans und seiner Substitutionsproducte. Ber. 24, 4140. Centr. B. 1892, I, 286.

1892.

A. Fock, Krystallographische—chemische Untersuchungen. Zeit. Kryst. 20, 332. Centr. B. 1892, II, 351.

1893.

C. Matignin, Ureides polybasiques et acide urique. Ann. chim. phys. (6) 28, 289. Centr. B. 1893, I, 692.

A. Pinner, Ueber Säurestofffreie Pyrimidine. Ber. 26, 2122. Centr. B. 1893, II, 811.

F. Lengfeld and J. Stieglitz, Derivatives of Nitrogen Halogen Compounds. Amer. Chem. J. 15, 221.

Ibid. (Second paper). Amer. Chem. J. 15, 517.

W. Traube, Ueber Guanidinderivative zweibasicher Säuren. Ber. 26, 2551. Centr. B. 1894, I, 23.

A. Kossell und A. Neumann, Ueber das Thymin ein Spaltungsproduct der Nucleinsäure. Ber. 26, 2753. Centr. B. 1894, I, 40.

1894.

W. Traube, Ueber Harnstoffderivate des Diacetonamins. Ber. 27, 277. Centr. B. 1894, I, 493.

A. Kossel und A. Neumann, Nucleinsäuren. Du Bois-Reymond's Arch. 1894, 194. Centr. B. 1894, I, 1158.

A. Kossel und A. Neumann, Darstellung und Spaltungsproducte der Nucleinsäure (Adenylsäure). Ber. 27, 2215. Centr. B. 194, II, 708.

A. Angeli Einwirkung der salpetrigen Säure auf Aminouracil und auf Aminoaceton. Gaz. 24, 2, 366. Cer. R. 1894, 894. Centr. B. 1894, II, 775.

W. Techow, Ueber die Verwandlungen des Dimethylalloxans. Ber. 27, 3082. Centr. B. 195, I, 30.

1895.

R. Andreasch, Ueber Dimethylviolursäure und Dimethyldilitursäure. Monats. 16, 17. Centr. B. 1895, I, 842.

A. Pinner. Ueber Imidoäther. Ber. 28, 473. Centr. B. 1895, I, 880.

R. Andreasch, Ueber Dimethylviolursäure und Dimethyldilitursäure. Monats. 16, 773. Centr. B. 1895, II, 920.

H. Weidel und L. Niemilowicz, Über die Bildung von Thiazolderivaten aus Harnsäure. Monats. 16, 721. Centr. B. 1895, II, 923.

E. Fischer und L. Ach, Ueber einige schwefelhaltige Verbindungen der Harnsäuregruppe. Ann. 288, 157. Centr. B. 1895, II, 1046.

1896.

H. Ritthausen, Wassergehalt und Reaction des Alloxantins. Ber. 29, 892. Centr. B. 1896, I, 992.

Ibid. Ueber Alloxantin als spaltungsproduct des convicins aus Sauböhen (Vicia Faba minor) und Wicken (Vicia sativa). Ber. 29, 894. Centr. B. 1896, I, 993.

A. Kossel, Ueber die Bildung von Thymin aus Fischsperma. Zeit. physiol. Chem. 22, 188. Centr. B. 1896, II, 386.

H. Weidel und E. Roithner, Ueber den Abbau einiger Säureamide (*B*-Lactylharnstoff). Monats. 17, 174.

W. Van Dam, De l'action des hypobromites alcalins sur la succindiamide. Rec. trav. chim. 15, 101. Centr. B. 1896, II, 587.

H. Ritthausen, Reactionen des Alloxantins aus convicin der Säubohnen und Wicken. Ber. 29, 2106. Centr. B. 1896, II, 27.

1897.

S. Ruhemann, Ueber die Bildung der Pyrimidone. Ber. 30, 821. Centr. B. 1897, I, 1047.

A. F. Holleman, Sur les acides nitrobarbiturique et dimethylnitrobarbiturique. Rec. trav. chim. 16, 162. Centr. B. 1897, II, 266.

S. Ruhemann und A. S. Hemmy, Zur Kenntniss der Pyrimidine. Ber. 30, 1488. Centr. B. 1897, II, 309.

R. Müller, Ueber die condensation von Guanidin und Harnstoff mit Oxalessigester. J. prakt. Chem. (2) 55, 505. Centr. B. 1897, II, 478.

K. Sembritzki, Ueber Malonyldiathylharnstoff und 1, 3-Diathylharnsäure. Ber. 30, 1814. Centr. B. 1897, II, 735.

W. Schacht, Aethylen-und Trimethylenharnstoff. Inaug. Diss. 1897, Marburg. Centr. B. 1897, II, 195. Arch. Pharm. 235, 441. Centr. B. 1897, II, 736.

E. Schmidt, Notiz über einige Schwefelharnstoffe. Arch. Pharm. 235, 435. Centr. B. 1897, II, 737.

P. Flatow, Ueber Cumenylimidoäther. Ber. 30, 2006. Centr. B. 1897, II, 756.

E. Fischer, Neue Synthese der Harnsäure des Hydroxycaffeins und des Aminodioxypurins. Ber. 30, 559.

S. Ruhemann und A. Hemmy, Weitere Studien über den Dicarboxylglutaconsäureester. Ber. 30, 2022. Centr. B. 1897, II, 861.

P. Fritsch, Ueber die Umwandlung des Pentachloracetons in Trichloracrylsäure und Monochlormalonsäure. Ann. 297, 312. Centr. B. 1897, II, 969.

O. Bromberg, Über die Verbindungen des Alloxans und Dimethylalloxans mit dem Semicarbazid. Ber. 30, 131.

Wolf v. Loeben, Ueber s-Methylharnsäure. Ann. 298, 181.

E. Fischer und H. Clemm, Ueber l-methyl und 1, 7-Dimethyl-Harnsäure. Ber. 30, 3089.

M. Frankel, Ueber Trimethylen-p-tolyldiamin und γ -Iodpropylamin. Ber. 30, 2947. Centr. B. 1897, II, 1144.

R. Müller, Einwirkung von Oxalessigester auf Guanidin und Harnstoffabkommlinge. J. prakt. Chem. 56, 475.

1898.

D. Vitali, Einige Beobachtungen über die Harnsäure und über die Murexid reaktion. Boll. chim. Farm. 37, 65. Centr. B. 1898, I, 665.

E. Schmidt, Ueber Pseudoharnstoffe. Arch. d. Pharm. 236, 441. Centr. B. 1898, II, 765.

O. Kühling, Ueber die Darstellung von Alloxanphenylhydrazon aus Barbitursäure. Ber. 31, 2110. Centr. B. 1898, II, 781.

H. L. Wheeler, Researches on the Cycloamidines: Pyrimidine Derivatives. Amer. Chem. Jour. 20, 481. Centr. B. 1898, II, 292.

1899.

S. Gabriel und J. Colman, Ueber das Pyrimidin. Ber. 32, 1525. Centr. B. 1899, II, 108.

W. Gulewitsch, Ueber das Arginin. Zeit. physiol. Chem. 27, 180.

Ibid. Ueber das Thymin. Zeit. physiol. Chem. 27, 292. Centr. B. 1899, II, 259.

J. Guinchard, Ueber die farbigen Salze aus Violursäure und anderen ring förmigen Oximidoketonen. Ber. 32, 1723. Centr. B. 1899, II, 290.

S. Gabriel und J. Colman, Zur Kenntnis der Abkömmlinge des 4-Methylpyrimidins. Ber. 32, 2921. Centr. B. 1899, II, 1103.

M. Scholtz, Sterische Hinderung chemischer Reaktionen. Ber. 32, 2251. Centr. B. 1899, II, 708. (N, N-Diphenylhexahydropyrimidine).

R. Behrend und R. Grünwald, Ueber Aminouracil. Ann. 309, 254. Centr. B. 1900, I, 21.

R. Behrend und E. Dietrich, Ann. 309, 260. Centr. B. 1900, I, 21.

W. Traube und H. Lorenz, Ueber Harnstoff und Thioharnstoffderivate des Diacetonamins. Ber. 32, 3156. Centr. B. 1900, I, 26.

W. Traube und M. Schall, Ueber Harnstoff und Guanidinderivate des Diacetonamins. Ber. 32, 3174. Centr. B. 1900, I, 27.

W. Traube und R. Schwarz, Ueber die Einwirkung von Amidinen auf Mesityloxyd und Phoron. Ber. 32, 3163. Centr. B. 1900, I, 29.

1900.

W. Jones, Ueber das Thymin. Z. physiol. Chem. 29, 20. Centr. B. 1900, I, 285.

R. Behrend und F. C. Meyer Ueber die Einwirkung von Phenylisocyanat auf Aminocrotonsäureester. Ber. 33, 621. Centr. B. 1900, I, 760.

E. Fischer, Ueber aromatische Derivate der Harnsäure. Sitzungsber. Berliner Akad. Wiss. Berlin 1900, 122. Ber. 33, 701. Centr. B. 1900, I, 806. (Uramil).

H. Steudel und A. Kossel, Ueber das Thymin. Z. physiol. Chem. 29, 303. Centr. B. 1900, I, 967.

W. Traube, Ueber eine neue Synthese des Guanins und Xanthins. Ber. 33, 1371. Centr. B. 1900, I, 1273.

R. Andreasch, Ueber Methylviolursäure und Methyl-dilitursäure. Monats. 21, 281. Centr. B. 1900, II, 41.

S. Ruhemann and H. E. Stapleton, Condensation of Ethyl Acetylenedicarboxylate with Bases and *B*-Ketonic Esters. Proc. Chem. Soc. 16, 121. J. Chem. Soc. 77, 804. Centr. B. 1900, II, 92, 477.

W. Jones, Ueber die Darstellung des Thymins. Z. physiol. Chem. 29, 461. Centr. B. 1900, II, 487.

H. Steudel, Ueber die constitution des Thymins. Z. physiol. Chem. 30, 539. Centr. B. 1900, II, 1152.

W. Traube, Der synthetische Aufbau der Harnsäure, des Xanthins, Theobromins Theophyllins und Caffeins aus der Cyanessigsäure. Ber. 33, 3035. Centr. B. 1900, II, 1207.

J. Tafel und A. Weinschenk, Elektrolytische Reduction des Methyluracils. Ber. 33, 3378. Centr. B. 1901, I, 100.

Ibid. Elektrolytische Reduction von Barbitursäure. Ber. 33, 3383. Centr. B. 1901, I, 101.

A. Ascoli, Ueber ein neues Spaltungsprodukt des Hefenucleins. Z. physiol. Chem. 31, 161. Centr. B. 1901, I, 127. (Discovery of Uracil).

S. Gabriel, Pyrimidin aus Barbitursäure. Ber. 33, 3666. Centr. B. 1901, I, 378.

- H. Steudel, Ueber die Constitution des Thymins. *Z. physiol. Chem.* 30, 539. *Centr. B.* 1901, I, 443; 1900, II, 1152.
E. F. Armstrong, Ueber 9-Athylharnsäure. *Ber.* 33, 2308.

1901.

- J. Tafel, Notiz über Hydrouracil. *Ber.* 34, 144. *Centr. B.* 1901, I, 508.

P. Koech (Behrend), Ueber Umwandlung der Isodialursäure in Dialursäure. *Ann.* 315, 246. *Centr. B.* 1901, I, 682.

C. v. Vogel (Behrend), Ueber die Condensation von Isodialursäure mit Thioharnstoff. *Ann.* 315, 259. *Centr. B.* 1901, I, 682.

E. Fischer und G. Roeder, Synthese des Thymins und anderer Uracile. *Sitzung. Kgl. Akad. Wiss. Berlin* 1901, 12; 268. *Centr. B.* 1901, I, 887.

H. Steudel, Das Verhalten einiger Pyrimidinderivate im Organismus. *Zeit. physiol. Chem.* 52, 285. *Centr. B.* 1901, I, 1235.

S. Gabriel und J. Colman, Synthesen in der Purinreihe. *Ber.* 34, 1234. *Centr. B.* 1901, I, 1279.

J. Tafel, Ueber die Tetrahydroharnsäure. *Ber.* 34, 1181. *Centr. B.* 1901, I, 1287.

A. Weinschenk, Ueber Condensation von Barbitursäure mit aromatischen Aldehyden zu gefärbten Substanzen. *Ber.* 34, 1685. *Centr. B.* 1901, II, 281.

T. Rapoport, Ueber einige Pyrimidine und Kyanidine aus dem Paranitrobenzamidin. *Ber.* 34, 1983. *Centr. B.* 1901, II.

G. Pellizzari und C. Roncagliolo, Ueber die isomeren Phenylamidoguanidine. *Gaz.* 31, 513. *Centr. B.* 1901, II, 591.

J. Schlenker, Ueber 4, 5-Dimethylpyrimidin. *Ber.* 34, 2812. *Centr. B.* 1901, II, 1047.

J. Tafel und L. Reindl, Elektrolytische Reduction einiger cyclischer Uräide. *Ber.* 34, 3286. *Centr. B.* 1901, II, 1154.

S. Gabriel, Amidoderivate des Pyrimidins. *Ber.* 34, 3362. *Centr. B.* 1901, II, 1172.

R. Behrend und H. Schreiber, Ueber Brom und Chloraminocrotonsäureester. *Ann.* 318, 371. *Centr. B.* 1901, II, 1334.

E. Fischer und G. Röeder, Synthese des Uracils, Thymins und Phenyluracils. *Ber.* 34, 3751. *Centr. B.* 1902, I, 53.

St. Augerstein, Ueber 4, 6-Dimethylpyrimidin. *Ber.* 34, 3956. *Centr. B.* 1902, I, 126.

A. Pinner, Ueber Pyridoylessigester. *Ber.* 34, 4234. *Centr. B.* 1902, I, 209.

W. O. Emery, Ueber Derivate des Pyrimidins. Ber. 34, 4178. Centr. B. 1902, I, 265.

E. Fischer und G. Roeder, Nachtrag zu der Mittheilung: Synthese des Uracils, Thymins und Phenyluracils. Ber. 34, 4129. Centr. B. 1902, I, 267.

A. Agrestini, Ueber einige Reaktionen des Alloxans und des Alloxantins. Boll. Chim. Farm. 41, 5. Centr. B. 1902, I, 631.

1902.

S. Gabriel und J. Colman, Zur Kenntniss der methylierten Pyrimidine. Ber. 35, 1569. Centr. B. 1902, I, 1235.

K. F. M. J. Schmidt, Zur Kenntniss der methylierten Pyrimidine. Ber. 35, 1575. Centr. B. 1902, I, 1237.

E. Fischer und H. Tüllner, Verwandlung der Isoharnsäure in Harnsäure und Thioxanthin. Ber. 35, 2563. Centr. B. 1902, II, 578.

R. Behrend und R. Thurm, Ueber die Constitution der Alkylderivate des Methyluracils und der 4-Methylharnsäure. Ann. 323, 160. Centr. B. 1902, II, 889.

R. Behrend und R. Grünwald, Ueber die Oxydation des Methyluracils. Ann. 323, 178. Centr. B. 1902, II, 890.

G. Wollers (Behrend), Ueber Diazoisonitrosomethyluracil und 4-Aminopyrazol. Ann. 323, 379. Centr. B. 1902, II, 1101.

F. Kunckell und L. Zumbusch, Ueber die Einwirkung von Mucobrom und Mucochlorsäure auf Benzamidin. Ber. 35, 3164. Centr. B. 1902, II, 1215.

F. Kunckell und O. Sarfert, Ueber die Einwirkung von Benzamidin auf *B*-Brom-*a*-Benzylacetophenon. Ber. 35, 3169. Centr. B. 1902, II, 1216.

F. Sachs und W. Lewin, Zur Kenntniss des *p*-dimethylamidobenzaldehyde. Ber. 35, 3569. Centr. B. 1902, II, 1385.

L. Kaess und J. Gruszhiewicz, Ueber die Verbindungen der Mesoxalsäure (Dioxymalonsäure) und Glyoxylsäure mit Guanidin. Ber. 35, 3600. Centr. B. 1902, II, 1411.

R. Andreasch, Zur Kenntniss des Lactylharnstoffes. Monats. 23, 803. Centr. B. 1902, II, 1416.

1903.

A. Kossel und H. Steudel, Ueber das Vorkommen des Uracils in Thierkörper. Zeit. physiol. Chem. 37, 245. Centr. B. 1903, I, 593.

A. Kossel und H. Steudel, Ueber das Cytosin. Zeit. physiol. Chem. 37, 377. Centr. B. 1903, I, 725.

P. A. Levene, Ueber das Vorkommen von Uracil bei der Pankreasautolyse. Zeit. physiol. Chem. 37, 527. Centr. B. 1903, I, 1218.

H. L. Wheeler and H. F. Merriam, On Some Condensation Products of the Pseudothioureas: Syntheses of Uracil, Thymine and Similar Compounds. *Amer. Chem. Jour.* 29, 478. *Centr. B.* 1903, I, 1308.

H. L. Wheeler and T. B. Johnson, Syntheses of Amino-oxy-pyrimidines having the Composition of Cytosine: 2-Amino-6-oxy-pyrimidine and 2-Oxy-6-aminopyrimidine. *Amer. Chem. Jour.* 29, 492. *Centr. B.* 1903, I, 1310.

Ibid. On Cytosine or 2-Oxy-6-aminopyrimidine from Tritico-nucleic Acid. *Amer. Chem. Jour.* 29, 505. *Centr. B.* 1903, I, 1311.

A. Kossel und H. Steudel, Weitere Untersuchungen über das Cytosin. *Zeit. physiol. Chem.* 38, 49. *Centr. B.* 1903, I, 365.

P. A. Levene, Darstellung und Analyse einiger Nucleinsäuren. *Zeit. physiol. Chem.* 38, 80. *Centr. B.* 1903, I, 1366.

F. Kutscher, Eine Methode zur Darstellung des Cytosins. *Zeit. physiol. Chem.* 38, 170. *Centr. B.* 1903, I, 1417.

A. Byk, Ueber einige Derivate des Pyrimidins. *Ber.* 36, 1915. *Centr. B.* 1903, II, 208.

E. Büttner, Einige Umsetzungen des 2, 4, 6-Trichlor-pyrimidins. *Ber.* 36, 2227. *Centr. B.* 1903, II, 449.

R. Behrend und L. Fricke, Ueber die Oxydation des Trimethyluracils. *Ann.* 327, 253. *Centr. B.* 1903, II, 349.

S. Gabriel und J. Colman, Zur Kenntniss des Pyrimidins und methylirter Pyrimidine. *Ber.* 36, 3379. *Centr. B.* 1903, II, 1192.

H. Steudel, Fütterungsversuche in der Pyrimidingruppe. *Zeit. physiol. Chem.* 39, 136. *Centr. B.* 1903, II, 591.

P. A. Levene, Darstellung und Analyse einiger Nucleinsäuren. *Zeit. physiol. Chem.* 39, 479.

S. Ruhemann, The Action of Benzamidin on *B*-Diketonic Olefines. *Proceedings Chem. Soc. (London)* 19, 246. *Centr. B.* 1904, I, 164.

/ 1904.

W. Traube. Der Aufbau der Xanthinbasen aus der Cyanessigsäure. Synthese des Hypoxanthins und Adenins. *Ann.* 331, 64. *Centr. B.* 1904, I, 1199.

W. M. Bruce, On the Oxygen Ethers of Ureas. *Jour. Amer. Chem. Soc.* 26, 419. *Centr. B.* 1904, I, 1558.

Ibid. *Jour. Amer. Chem. Soc.* 26, 449. *Centr. B.* 1904, II, 29.

H. L. Wheeler and T. B. Johnson, 5-Methylcytosine. *Amer. Chem. Jour.* 31, 591. *Centr. B.* 1904, II, 240.

M. Slimmer and J. Stieglitz, The Constitution of Purpuric

Acid and of Murexide. Amer. Chem. Jour. 31, 661. Centr. B. 1904, II, 316.

O. Piloty, Ueber die Harnsäuregruppe. Ann. 333, 22. Centr. B. 1904, II, 768.

Ibid. Ann. 333, 71. Centr. B. 1904, II, 826.

R. Möhlau, Ueber die Constitution der Purpursäure und des Murexids. Ber. 37, 2686. Centr. B. 1904, II, 829.

T. B. Johnson and S. H. Clapp, Synthesis of 2-Amino-5-Methyl-6-Oxyprimidine. Amer. Chem. Jour. 32, 130. Centr. B. 1904, II, 955.

R. Burian, Zur Frage der Bindung der Purinbasen im Nucleinsäuremolekül. Zeit. physiol. Chem. 42, 297. Centr. B. 1904, II, 996.

E. Fischer und A. Dilthey, Ueber C-Dialkylbarbitursäuren und über die Ureide der Dialkylelessigsäuren. Ann. 335, 334. Centr. B. 1904, II, 1381.

H. L. Wheeler and G. S. Jamieson, 2-Oxy-4, 6-Diaminopyrimidine. Amer. Chem. Jour. 32, 342. Centr. B. 1904, II, 1413.

S. Gabriel, Ueber 2-Methylpyrimidin. Ber. 37, 3638. Centr. B. 1904, II, 1415.

S. Gabriel und J. Colman, Zur Darstellung des 2, 4, 6-Trichlorpyrimidin. Ber. 37, 3657. Centr. B. 1904, II, 1416.

E. Fischer und A. Dilthey, Ueber C-Dialkylbarbitursäuren und über die Ureide der Dialkylelessigsäuren. Ann. 336, 345. Centr. B. 1904, II, 1713.

W. Traube, Ueber 2-Amino-Adenin. Ber. 37, 4544. Centr. B. 1905, I, 160.

1905.

S. Gabriel, Zur Geschichte der Aminopyridine (Aminopyrimidine). Ber. 38, 149. Centr. B. 1905, I, 459.

S. Gabriel, Ueber Isocystein und Isocystin. Ber. 38, 630. Centr. B. 1905, I, 807.

S. Gabriel, Notizen über Bromdihydrouracil. Ber. 38, 1689. Centr. B. 1905, I, 1536.

H. L. Wheeler and H. S. Bristol, The Structure of Some Substitution Products. Amer. Chem. Jour. 33, 437. Centr. B. 1905, I, 1709.

Ibid. The Action of Potassium Thiocyanate Upon Some Imide Chlorides. Amer. Chem. Jour. 33, 448. Centr. B. 1905, I, 1711.

T. Posner, Zur Kenntniss der *B*-Aminosäuren. Ber. 38, 2316. Centr. B. 1905, II, 479.

R. Bartling (Behrend), Nachtrag zu der Abhandlung:

Ueber die condensation von Isodialursäure mit Thioharnstoff. Ann. 339, 37.

M. Conrad, Ueber Iminobarbitursäuren und Barbitursäuren. Ann. 340, 310. Centr. B. 1905, II, 889.

M. Conrad und A. Zart, Ueber Iminodialkylmalonylalkyl und Phenylharnstoffe. Ann. 340, 326.

Ibid. Ueber Cyandialkylacetylharnstoffe und über die Amide substituierter Malonsäuren und Cyanessigsäuren. Ann. 340, 335. Centr. B. 1905, II, 891.

O. Kühling, Ueber condensationsproducte des Alloxans mit gesättigten Ketonen. Ber. 3003. Centr. B. 1905, II, 1240.

P. A. Levene, Darstellung und Analyse einiger Nucleinsäuren. Milznucleinsäure. Zeit. physiol. Chem. 45, 370. Centr. B. 1905, II, 1502.

T. B. Johnson and C. O. Johns, The Action of Aqueous and Alcoholic Ammonia, and Aniline on Some Halogen and Mercapto Pyrimidines. Amer. Chem. Jour. 34, 175. Centr. B. 1905, II, 1353.

T. B. Johnson, 2-Ethylmercapto-5-amino-6-oxypyrimidine. Amer. Chem. Jour. 34, 191. Centr. B. 1905, II, 1499.

O. Gerngross, Ueber eine Synthese des Thymins. Ber. 38, 3408. Centr. B. 1905, I, 1605.

H. Steudel, Zur Kenntniss der Thymusnucleinsäuren. Zeit. physiol. Chem. 46, 332. Centr. B. 1906, I, 142.

W. N. Hartley, The Absorption Spectra of Uric Acid, Murexide and the Ureides in Relation to Color and their Chemical Structure. Jour. Chem. Soc. (London), 87, 1796.

H. Osten (R. Behrend), Ueber Trioxydihydromethyluracil. Ann. 343, 133. Centr. B. 1906, I, 749.

C. Hufschmidt (R. Behrend), Die Oxydation der methylylirten Uracile. Ann. 343, 155.

Ibid. Nitriung des Trimethyluracils. Ann. 343, 168.

A. Einhorn, Ueber die N-Methylolverbindungen der Säureamide. Ann. 343, 207.

E. von Meyer, Ueber die Konstitution und Bildungsweise der Kyanalkine genannten trimolekularen Nitrile. Ber. K. sächs. Ges. Wiss. math. phys. 57, 324. Centr. B. 1906, I, 941.

T. B. Johnson and C. O. Johns, On 2, 5-Diamino-6-oxypyrimidine. Am. Chem. Jour. 34, 554. Centr. B. 1906, I.

1906.

O. Isay, Eine synthese des Purins. Ber. 39, 250. Centr. B. 1906, I, 659.

W. Traube und W. Nithack, Ueber die Einwirkung von

Aldehyden auf Orthodiamine der Pyrimidinreihe. Ber. 39, 227. Centr. B. 1906, I, 687.

R. Behrend und H. Friedrich, Zur Kenntniss der Dialursäure. Ann. 344, 1. Centr. B. 1906, I, 1007.

R. Behrend und H. Hennicke, Ueber die Einwirkung von Senfölen auf Aminocrotonsäureester. Ann. 344, 19. Centr. B. 1906, I, 1007.

W. Traube und F. Winter, Synthese des 3-Methylhypoxanthins. Arch. d. Pharm. 244, 11. Centr. B. 1906, I, 1337.

J. A. Mandel und P. A. Levene, Darstellung und Analyse einiger Nukleinsäuren: Ueber die Nukleinsäure der Niere. Zeit. physiol. Chem. 47, 140. Centr. B. 1906, I, 1363.

T. B. Johnson and C. O. Johns, Some 5-Iodopyrimidin Derivatives. 5-Iodocytosin. Jour. Biolog. Chem. 1, 305. Centr. B. 1906, I, 1889.

R. Möhlau und H. Litter, Zur Frage der Konstitution des Murexids und der Purpursäure. Jour. prakt. Chem. 73, 449. Centr. B. 1906, II, 503.

Ibid. Ueber die Einwirkung primärer Amine auf Alloxantin. Jour. prakt. Chem. 73, 472. Centr. B. 1906, II, 504.

T. B. Johnson and E. V. McCollum, On Methods of Synthesizing Isobarbituric Acid and 5-Oxycytosin. Jour. Biolog. Chem. 1, 437. Centr. B. 1906, I, 889.

T. B. Johnson and E. V. McCollum, The Action of Potassium Thiocyanate Upon Imide Chlorides. Amer. Chem. Jour. 36, 136. Centr. B. 1906, II, 1063.

T. B. Johnson and E. V. McCollum, On The Formation of Purines from Urea Pyrimidines. Amer. Chem. Jour. 36, 149. Centr. B. 1906, II, 1064.

T. B. Johnson, C. O. Johns, and F. W. Heyl, On 5-Nitrocytosine and Its Reduction to 2-Oxy-5, 6-Diaminopyrimidine. Amer. Chem. Jour. 36, 160. Centr. B. 1906, II, 1066.

T. B. Johnson and G. A. Menge, 5-Ethylcytosin. Jour. Biolog. Chem. 2, 105. Centr. B. 1906, II, 1507.

H. Steudel, Ueber die Oxydation der Nucleinsäure. Zeit. physiol. Chem. 48, 425.

M. A. Whitely, 1, 3-Diphenylbarbituric Acid and Some Colored Derivatives of the Same. Synthesis of 1, 3-Diphenyluric Acid. Proceedings Chem. Soc. (London), 22, 200. Centr. B. 1906, II, 1404.

J. K. Wood, The Acidic Constants of Some Ureides and Uric Acid Derivatives. Jour. Chem. Soc. (London), 89, 1831. Centr. B. 1907, I, 539.

P. A. Levene und J. A. Mandel, Darstellung und Analyse einiger Nucleinsäuren. Nucleinsäure der Spermatozoen des Maifisches. Zeit. physiol. Chem. 50, 1. Centr. B. 1907, I, 354.

J. A. Mandel and P. A. Levene, On the Pyrimidine Bases of the Nucleic Acid Obtained from Fish Eggs. *Jour. Biolog. Chem.* 1, 425. *Centr. B.* 1906, I, 1790.

1907.

H. Burrows and C. A. Keane, The Condensation of Diethylmalonamide with Aldehydes. *Jour. Chem. Soc. (London)*, 91, 269. *Centr. B.* 1907, I, 1270.

H. L. Wheeler, T. B. Johnson and C. O. Johns, Synthesis of Uracil-5-carboxylic Acid. *Amer. Chem. Jour.* 37, 392. *Centr. B.* 1907, I, 1632.

E. F. J. Atkinson, H. Ingham and J. F. Thorpe, The Formation and Reactions of Iminocompounds. The Formation of 1, 3-Naphthylenediamine and Its Derivatives* from o-Tolunitrile. *Jour. Chem. Soc. (London)*, 91, 583. *Centr. B.* 1907, II, 69.

R. Burian, Weitere Beiträge zur Kenntniss der Diazoaminoverbindungen der Purinbasen. *Zeit. physiol. Chem.* 51, 425.

Ibid. Pyrimidinderivate aus Purinbasen. *Ziet. physiol. Chem.* 51, 438. *Centr. B.* 1907, II, 141.

R. Behrend und O. Hoebel, Ueber Alkylderivate des Methyluracils. *Ann.* 353, 242. *Centr. B.* 1907, II, 304.

R. Behrend und G. Offe, Ueber die Oxydation von Uracilderivaten. *Ann.* 353, 267. *Centr. B.* 1907, II, 305.

T. B. Johnson and F. W. Heyl, Some Condensation Products of a Substituted Pseudothiourea: Synthesis of 1-Methyluracil. *Amer. Chem. Jour.* 37, 628. *Centr. B.* 1907, II, 449.

S. J. M. Auld, Mercury Derivatives of Pseudo Acids Containing the Group CONH. *Jour. Chem. Soc. (London)*, 91, 1045. *Centr. B.* 1907, II, 831.

P. A. Levene, Notiz über die Pikrolonate einiger Nucleinbasen. *Biochem. Zeit.* 4, 320. *Centr. B.* 1907, II, 587.

Ibid. Ueber die diuretische Wirkung des Thymins. *Biochem. Zeit.* 4, 316. *Centr. B.* 1907, II, 619; also *Jour. Exper. Medicine*, 9, 229.

W. Gössling, Dialkylbarbitursäuren. *Chem. Ztg.* 31, 711. *Centr. B.* 1907, II, 689.

M. A. Whiteley, Studies in the Barbituric Acid Series. 1, 3-Diphenylbarbituric Acid and Some Coloured Derivatives. *Jour. Chem. Soc. (London)*, 91, 1330. *Centr. B.* 1907, II, 1065.

H. L. Wheeler and T. B. Johnson, On a Color Test for Uracil and Cytosin. *Jour. Biolog. Chem.* 3, 183. *Centr.* 1907, II, 1087.

A. P. N. Franchimont and H. Friedmann, L'action de l'acide azotique reel sur la trimethylene-ureine et sur l'hydrouracil. *Rec. trav. chim.* 26, 218. *Centr. B.* 1907, II, 1248.

J. Tafel und P. A. Houseman, Zur Kenntniss des Isopurons. Ber. 40, 3743. Centr. B. 1907, II, 1401.

H. L. Wheeler, On Some Salts of Cytosin, Isocytosin, 6-Aminopyrimidin and 6-Oxypyrimidin. Jour. Biolog. Chem. 3, 285.

H. L. Wheeler, Uracil-4-Carboxylic Acid. Amer. Chem. Jour. 38, 358. Centr. B. 1907, II, 1634.

T. B. Johnson and F. W. Heyl, The Action of Methyl Iodide on 2-Anilino-6-oxypyrimidine, and the Synthesis of 2-Anilinoxyprimidine. Amer. Chem. Jour. 38, 237. Centr. B. 1907, II, 1248.

T. B. Johnson, Synthesis of Thymin 4-Carboxylic Acid. Jour. Biolog. Chem. 3, 299. Centr. B. 1907, II, 1531.

H. L. Wheeler and C. O. Johns, Synthesis of Cytosine-5-Carboxylic Acid. Amer. Chem. Jour. 38, 594. Centr. B. 1908, I, 289.

T. B. Johnson and C. F. Speh, Synthesis of Thymine-5-Carboxylic Acid. Amer. Chem. Jour. 38, 602. Centr. B. 1908, I, 390.

T. B. Johnson and F. W. Heyl, Synthesis of 4-Methyluracil-5-Acetic Acid. Amer. Chem. Jour. 38, 659. Centr. B. 1908, I, 391.

M. Conrad, Zur Kenntniss der Hydurilsäure. Ann. 356, 24. Centr. B. 1907, II, 1609.

U. Suzuki, K. Aso und H. Mitarai, Ueber die chemische Zusammensetzung der japanischen Sojasauce oder Schoyü. Bull. college Agric. Tokio, 7, 477. Centr. B. 1907, II, 1649.

J. Tafel und H. B. Thompson, Elektrolytische Reduktion der Aethylbarbitursäuren. Ber. 40, 4489. Centr. B. 1908, I, 122.

H. Steudel, Ueber die Bildung von Pyrimidinderivate aus Purinkörpern. Zeit. physiol. Chem. 53, 508. Centr. B. 1908, I, 123.

A. Einhorn und H. v. Diesbach, Ueber die Reduktion der Diäthylthiobarbitursäure. Ber. 40, 4902. Centr. B. 1908, I, 455.

H. L. Wheeler and G. S. Jamieson, On Some Picrolonates. Jour. Biolog. Chem. 3, 111.

1908.

F. Sachs und E. Appenzeller, Ueber den Tetramethyl-2,4-diaminobenzaldehyde. Ber. 41, 91. Centr. B. 1908, I, 519.

R. Majima, Ueber die Kondensation der Alkylguanidine mit Acetessigester usw. Ber. 41, 176. Centr. B. 1908, I, 1044.

F. Baum, Zur Kenntniss der Träubeschen Pyrimidin-synthesen. Ber. 41, 532. Centr. B. 1908, I, 1167.

S. Gabriel, Über einige synthetisch verwerthbare Derivate der Aminosäuren. Ber. 41, 242. Centr. B. 1908, I, 729.

A. Einhorn, Ueber neue Arzneimittel. Ann. 359, 145. Centr. B. 1908, I, 1535.

P. A. Levene und J. A. Mandel, Zur Herkunft des Cytosins beider Hydrolyse der tierischen Nucleinsäuren. Biochem. Zeit. 9, 233. Centr. B. 1908, I, 1710.

T. B. Osborne and F. W. Heyl, The Pyrimidine Derivatives in Nucleic Acid. Amer. Jour. of Physiol. 21, 157.

T. de Haan, La condensation β -dicetones avec l'uree. Rec. trav. chim. 27, 162. Centr. B. 1908, II, 35.

O. Kuhling, Über Phenacyldialursäure, Tartronursäure und Isohydantoinsäure. Ber. 41, 1658. Centr. B. 1908, II, 53.

F. Pohl, Zur Kenntniss des Dicyandiamids. Jour. pr. Chem (2) 77, 533. Centr. B. 1908, II, 151.

P. A. Levene und J. Mandel, Über die Konstitution der Thymonucleinsäure. Ber. 41, 1905. Centr. B. 1908, II, 424.

R. Behrend und K. Beer, Über Trioxydihydromethyluracil. Ann. 362, 115. Centr. B. 1908, II, 886.

T. B. Johnson, A Method of Separating Thymin from Uracil. Jour. Biol. Chem. 4, 407. Centr. B. 1908, II, 1043.

T. B. Johnson, The Action of Nitric Acid on 2, 6-Dioxy-pyrimidines. Oxynitrohydrothymine. Amer. Chem. Jour. 40, 19. Centr. B. 1908, II, 802.

L. Hugouneng et A. Morel, Contribution a l'etude de la constitution des nucleoproteides. Recherches sur les constituants de la pepsine. Compt. rend. 147, 212. Centr. B. 1908, II, 805.

H. L. Wheeler and L. M. Liddle, Synthesis of Uracil-3-acetic Acid. Jour. Amer. Chem. Soc. 30, 1152. Centr. B. 1908, II, 1045.

Ibid: Synthesis of Uracil-4-acetic Acid. Jour. Amer. Chem. Soc. 30, 1156. Centr. B. 1908, II, 1045.

T. B. Johnson and S. H. Clapp, Syntheses of Some Nitrogen-Alkyl Derivatives of Cytosine, Thymine and Uracil. Jour. Biol. Chem. 5, 49. Centr. B. 1908, II, 1264.

T. B. Johnson and S. H. Clapp, The Action of Diazo-Benzene Sulphonic Acid on Thymin, Uracil and Cytosin. Jour. Biol. Chem. 5, 163. Centr. B. 1908, II, 1872.

J. Mandel, Jacobs and P. Levene, On Nucleic Acids. Proceedings Soc. Exp. Biol. Med. 5, 92.

T. B. Johnson and W. F. Storey, The Action of Potassium Thiocyanate Upon Some Imide-Chlorides. Amer. Chem. Jour. 40, 131. Centr. B. 1908, II, 1105.

E. L. Pinner, *Über 2-Phenyl-4,6-dioxypyrimidine, Malonylbenzamidine.* Ber. 41, 3517. Centr. B. 1908, II, 1692.

H. L. Wheeler and C. O. Johns, *Synthesis of Cytosine-5-Carboxamide.* Amer. Chem. Jour. 40, 234. Centr. B. 1908, II, 1781.

C. O. Johns, *Synthesis of 4-Methylcytosine.* Amer. Chem. Jour. 40, 348. Centr. B. 1908, II, 1933.

T. B. Johnson and J. H. Derby, Jr., *Syntheses of Some Benzyl Derivatives of Uracil and Thymine.* Amer. Chem. Jour. 40, 444. Centr. B. 1909, I, 85.

F. Sachs und G. Meyerheim, *Über Azinpurine.* Ber. 41, 3957. Centr. B. 1909, I, 31.

T. B. Johnson and D. B. Jones, *Synthesis of new Derivatives of 5-Hydroxyuracil (Isobarbituric Acid).* Amer. Chem. Jour. 40, 538. Centr. B. 1909, I, 193.

H. L. Wheeler and L. M. Liddle, *Thio Derivatives of Uracil and the Preparation of Uracil in Quantity.* Amer. Chem. Jour. 40, 547. Centr. B. 1909, I, 447.

1909.

M. Engelmann, *Über eine Synthese des 1-Methylxanthins.* Ber. 42, 177. Centr. B. 1909, I, 524, 806.

A. Guyot et E. Michel, *Condensation des éthers mesoxaliques avec les amines aromatique tertiaires.* Compt. rend. 148, 229.

C. O. Johns, *On the Formation of Purine Derivatives from 4-Methyl Cytosine.* Amer. Chem. Jour. 41, 58. Centr. B. 1909, I, 925.

M. Conrad und A. Schulze, *Über Malonylamidderivate.* Ber. 42, 729. Centr. B. 1909, I, 1087.

O. Stark, *Zur Konstitution des Acetylacetonharnstoffs (4, 6-Dimethyl-2-ketopyrimidin).* Kondensation mit aromatischen Aldehyden. Ber. 42, 699. Centr. B. 1909, I, 1243.

Ibid: *Zur Konstitution des Acetylacetonharnstoffs. Einwirkung von Brom auf Acetylacetonharnstoff und seine Kondensationsprodukte mit Aldehyden.* Ber. 42, 708. Centr. B. 1909, I, 1245.

E. Fourneau, *Sur les acides oxyamines. Derives amines de l'acide oxyisobutyrique.* Bull. soc. chim. (4) 5, 229. Centr. B. 1909, I, 1318 (Hydrothymine).

A. Hantzsch, *Über Pantochromie und Chromoisomerie von Violuraten und verwandten Oximinoketonsalzen.* Ber. 42, 966. Centr. B. 1909, I, 1390.

A. Hantzsch und B. Issaias, *Über polychrome und Ester der Violursäuregruppe.* Ber. 42, 986. Centr. B. 1909, I, 1393.

H. Hantzsch und B. Issaias, Über polychrome und chromotrope Violurate. Ber. 42, 1000. Centr. B. 1909, I, 1395.

R. Behrend und R. Schultz, Über die Oxydation des Harnsäure in alkalischer Lösung. Ann. 365, 21. Centr. B. 1909, I, 1378.

O. Kühling und B. Schneider, Über Kondensationsprodukte des Alloxans. Ber. 42, 1285. Centr. B. 1909, I, 1548, 1952.

F. G. Dunan and W. Schneider, The Colour of Aqueous Solutions of Violuric Acid. Jour. Chem. Soc. (London), 95, 956. Centr. B. 1909, II, 348.

J. K. Wood and E. A. Anderson, The Constitution of the Salts of Barbituric Acid. Jour. Chem. Soc. (London), 95, 979. Centr. B. 1909, II, 426.

T. B. Johnson and D. B. Jones, Synthesis of 1-Methyl-5-oxyuracil. Jour. Amer. Chem. Soc. 31, 590. Centr. B. 1909, II, 545.

J. Posner und K. Rohde, Beiträge zur Kenntniss der ungesättigten Verbindungen. Über die Addition von Hydroxylamin auf ungesättigte Säuren mit Konjugierten Doppelbindungen. Ber. 42, 2785. Centr. B. 1909, II, 705. (Cinnamenyldihydrouracil).

H. L. Wheeler and T. B. Johnson, The Preparation of 3-Methyl and 3-Benzyluracil. Amer. Chem. Jour. 42, 30. Centr. B. 1909, II, 1047.

H. L. Wheeler and D. F. McFarland. The Preparation of 1, 4-Dimethyluracil and the Monobenzyl Derivatives of 4-Methyluracil. Amer. Chem. Jour. 42, 101. Centr. B. 1909, II, 1048.

T. B. Johnson and H. H. Guest, Sulphur Derivatives of 5-Oxyuracil. Preparation of 5-Benzylmercaptouracil and 5-Benzylmercaptocytosine. Amer. Chem. Jour. 42, 271. Centr. B. 1909, II, 1637.

T. B. Johnson and K. G. Mackenzie, Dimethyl Derivatives of 2-Aminopyrimidine. Preparation of 2-Methylamino-5-Methylpyrimidine. Amer. Chem. Jour. 42, 353. Centr. B. 1910, I, 284.

H. L. Wheeler and D. F. McFarland, The Action of Methyl Iodide and of Benzyl Chloride Upon 2-Oxy-4-Methyl-6-Methylmercaptopyrimidine. Amer. Chem. Jour. 42, 431. Centr. B. 1910, I, 1030.

T. B. Johnson, Synthesis of 5-Cyanuracil. Amer. Chem. Jour. 42, 505.

H. L. Wheeler and D. F. McFarland, The Thio Deriva-

tives of Thymine and the Preparation of Thymine. Amer. Chem. Jour. 43, 19.

C. Bülow und K. Haas, Synthetische Versuche zur Darstellung von Derivaten des heterokondensierten heterocyclischen 1, 3-Triazo-7, 0-pyrimidins. Ber. 42, 4638. Centr. B. 1910, I, 286.

J. Zerewitinow, Über die organischen Salze der Violursäure. Ber. 42, 4802. Centr. B. 1910, I, 342.

PATENTS

1900.

Centr. B. 1. 113.

1901.

Centr. B. I. 547, 1219.

1902.

Centr. B. II. 1165, 1229.

1903.

Centr. B. II. 778, 813, 1483.

1904.

Centr. B. I. 68, 69, 619.

“ II. 1631.

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“ II. 182, 728, 798, 1141, 1756.

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“ II. 198, 276, 655, 956, 2001.

1908.

Centr. B. I. 919.

1909.

Centr. B. I. 233, 1283.

“ II. 1182.







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